Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence Review of Specialist Cardiac Services

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About the Health Information and Quality Authority

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Foreword

Heart problems are associated with significant morbidity and mortality for individuals and can place a considerable economic burden on healthcare systems and society. High quality specialist cardiac services are crucial for providing the best possible outcomes for patients with heart problems. However, the organisation of these services nationally is complex and there are many different factors to consider. It is therefore important that the organisation of specialist cardiac services on a national level is informed by the best available evidence.

The National Review of Specialist Cardiac Services (referred to in this report as the National Review), which convened in January 2018, is an independently chaired review of national clinical cardiac services in Ireland. The National Review aims to recommend the best configuration for a national adult specialist cardiac service with population-based regional specialist cardiac networks and network hospitals.

An evidence review incorporating rigorous systematic reviews was undertaken by the Evidence for Policy Team within the HTA Directorate in HIQA to inform the work of the National Review.

HIQA would like to thank its Evaluation Team along with members of the National Review Steering Group who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

About Evidence for Policy

The Evidence for Policy Team was established within the Health Technology Assessment (HTA) Directorate of the Health Information and Quality Authority (HIQA) in 2018 following a request from the National Patient Safety Office (NPSO) in the Department of Health. The Evidence for Policy Team is responsible for implementing evidence synthesis programmes to deliver high-quality evidence to support the development of policy by the Department of Health.

Membership of the Evaluation Team

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Conflict of Interest

The evaluation team declared no conflict of interest.

Table of Contents

About the Health Information and Quality Authority 2
Foreword 3
About Evidence for Policy 4
Membership of the Evaluation Team 4
Funding 4
Conflict of Interest 4
List of Tables 10
List of Figures 11
List of Abbreviations 14
Executive Summary 19
Plain English Summary 32
1 Introduction 36
1.1 Background to the request 36
1.2 Description of the intervention 37
1.3 Purpose of the evidence review 38
1.4 Overall methodological approach for the evidence review 39
2 Review question one: international models of specialist cardiac networks 41
2.1 Introduction 41
2.2 Methods 43
2.2.1 Review question 43
2.2.2 Methods 43
2.2.3 Search strategy 45
2.2.4 Selection criteria 45
2.2.5 Data extraction and management 47
2.2.6 Quality appraisal/risk of bias assessment 48
2.2.7 Data synthesis 48
2.2.8 Protocol deviations 48
2.3 Results 48
2.3.1 Search results 48

2.3.2 Characteristics of included networks 49
2.3.3 Cardiac network types 52
2.3.4 Country of networks 52
2.3.5 Year of network establishment 52
2.3.6 Configuration of networks 52
2.3.7 Distances between hospitals in networks 54
2.3.8 Population served by networks 54
2.3.9 Monitoring of outcomes 55
2.3.10 Author reported findings 55
2.3.11 Components of the networks 56
2.3.12 Case study one: Emilia-Romagna Acute Coronary Syndrome Network 58
2.3.13 Case study two: Catalonia Codi Infart STEMI network 61
2.3.14 Case study three: Strategic Clinical Networks in England 62
2.4 Discussion 64
2.5 Conclusion 68
2.6 Key points 69

3 Review question two: organisational and service specification recommendations for centres providing percutaneous coronary interventions (PCI) 70
3.1 Introduction 70
3.2 Methods 71
3.2.1 Review question 71
3.2.2 Search strategy 71
3.2.3 Selection criteria 72
3.2.4 Data extraction and management 73
3.2.5 Quality appraisal 74
3.2.6 Assessment of currency and content 74
3.2.7 Protocol deviations 74
3.3 Results 74
3.3.1 Search results 74
3.3.2 Characteristics of included guidance documents 76
3.3.3 Primary Outcomes 80
3.3.4 Methodological quality of included studies 115

3.4 Discussion 120
3.5 Conclusions 123
3.6 Key points 124
4 Review question three: PCI volume-outcome relationship 126
4.1 Introduction 126
4.2 Methods 126
4.2.1 Review question 126
4.2.2 Search strategy 127
4.2.3 Selection criteria 127
4.2.4 Data extraction and management 128
4.2.5 Quality appraisal 129
4.2.6 Data synthesis 130
4.2.7 Assessing the certainty of the body of evidence using the GRADE approach 132
4.2.8 Protocol deviations 133
4.3 Results 134
4.3.1 Search results 134
4.3.2 Characteristics of included studies 135
4.3.3 Primary outcomes 147
4.3.4 Secondary outcomes 161
4.3.5 Methodological quality of included studies 164
4.3.6 Certainty of the evidence 167
4.4 Discussion 169
4.5 Key points 175
5 Review question four: pharmacoinvasive strategy versus primary PCI for STEMI 177
5.1 Introduction 177
5.2 Methods 178
5.2.1 Review question 178
5.2.2 Search strategy 179
5.2.3 Selection criteria 180
5.2.4 Data extraction and management 182

5.2.5 Risk of bias and quality appraisal 184
5.2.6 Data synthesis 184
5.2.7 Assessing the certainity of the body of evidence using the GRADE approach 186
5.2.8 Protocol deviations 186
5.3 Results 187
5.3.1 Search results 187
5.3.2 Characteristics of included studies 188
5.3.3 Primary effectiveness outcomes 200
5.3.4 Primary safety outcomes 205
5.3.5 Subgroup and sensitivity analyses 210
5.3.6 Secondary outcomes 210
5.3.7 Timing effects 212
5.3.8 Methodological quality of included studies 213
5.3.9 Certainty of the evidence 216
5.3.10 Ongoing studies 216
5.4 Discussion 216
5.5 Key points 222
6 Discussion 224
7 Summary of key outcomes from evidence reviews 236
References 238
Appendices 259
Appendix 1 — Search terms for electronic databases 259
Appendix 2 — Grey literature sources 265
Appendix 3 — Table of characteristics and outcomes 268
Appendix 4 — Recommendations from guidance documents included in RQ2 341
Appendix 5 — Guidance documents with recommendations on time-to-treatment only or for specific conditions/procedures or new PCI centres (RQ2) 378
Appendix 6 — Studies excluded after full-text review 396
Appendix 7 — Meta-regression (RQ3) 453
A7.1: Total PCI hospital volume 453
A7.2: Total PCI operator volume 455

A7.3: Primary PCI hospital volume 457

Appendix 8 — Sensitivity and subgroup analyses 459

A8.1 Total PCI Hospital Volume (RQ3) 459

A8.2 Total PCI Operator Volume (RQ3) 468

A8.3 Primary PCI Hospital Volume (RQ3) 473

A8.4 Sensitivity and subgroup analyses for RQ4 480

Appendix 9 — GRADE summary of findings table (RQ4) 481

Appendix 10 — Protocol deviations 486

List of Tables

Table 2.1: PICo for RQ1 43
Table 2.2: Inclusion and exclusion criteria for RQ1 46
Table 2.3: Table of characteristics of included acute coronary syndrome-related networks 50
Table 2.4: Table of characteristics of other (not ACS-related) included cardiac networks 51
Table 3.1: PICo for RQ2 71
Table 3.2: Inclusion and exclusion criteria for RQ2 72
Table 3.3 Table of characteristics of included guidance documents 77
Table 3.4: Organisational and service specification recommendations for centres providing PCI 92
Table 3.5 Quality appraisal of guidance documents presented as scaled domain scores using AGREE-II instrument 116
Table 4.1: PICOS for RQ3 126
Table 4.2: Inclusion and exclusion criteria for RQ3 128
Table 4.3: Definitions of the quality rating of evidence grades 133
Table 4.4: Table of characteristics of included studies for RQ3 136
Table 4.5: Summary of findings table for primary outcomes regarding the relationship between PCI procedural volume and postoperative (in-hospital or 30-day) mortality 168
Table 5.1: PICOS for RQ4 179
Table 5.2: Inclusion and exclusion criteria for RQ4 181
Table 5.3: Table of characteristics of included studies for RQ4 189

List of Figures

Figure 2.1: Hub and spoke model 42
Figure 2.2: PRISMA flow chart of included studies in RQ1 49
Figure 2.3: Map of the Emilia-Romagna Region in Italy 59
Figure 2.4: The hub and spoke network of Bologna province. 60
Figure 2.5: Map of Catalonia Region in Spain 61
Figure 3.1 PRISMA flow chart of included guidance documents for RQ2 76
Figure 3.2 Quality appraisal of guidance documents presented as the scaled domain score using the AGREE-II instrument 118
Figure 4.1: PRISMA flow chart of included studies for RQ3 135
Figure 4.2: Flow diagram of hospital-level studies 143
Figure 4.3: Flow diagram of operator-level studies 144
Figure 4.4: Results of the meta-analysis investigating the relationship between hospital volume and mortality, for total PCI procedures 147
Figure 4.5: Subgroup analysis examining the distribution of pooled effect sizes according to the risk of bias of included studies 148
Figure 4.6: Subgroup analysis examining the distribution of pooled effect sizes according to the completeness of case-mix adjustment 149
Figure 4.7: Results of the sensitivity analysis investigating the relationship between hospital volume and mortality, for all PCI procedures, when Inohara et al. is excluded 150
Figure 4.8: Cumulative meta-analysis investigating the relationship between hospital volume and mortality, for total PCI procedures 151
Figure 4.9: Sensitivity analysis without Inohara et al. for study period 152
Figure 4.10 Meta-regression plot examining relationship between median study period and the log of the effect size for high PCI volume hospitals, without Inohara et al. 153
Figure 4.11: Results of the meta-analysis investigating the relationship between operator volume and mortality, for all PCI procedures 154
Figure 4.12: Results of the meta-analysis investigating the relationship between operator volume and mortality, for all PCI procedures, when Badheka et al. is

excluded..... 155
Figure 4.13: Results of the meta-analysis investigating the relationship between operator volume and mortality, for all PCI procedures, when Fanaroff et al. is excluded..... 155
Figure 4.14: Results of the meta-analysis investigating the relationship between hospital volume and mortality, for primary PCI procedures 156
Figure 4.15: Subgroup analysis examining the distribution of pooled effect sizes according to the mortality outcome used 157
Figure 4.16: Results of the meta-analysis investigating the relationship between hospital volume and mortality, for primary PCI procedures, when Navarese et al. is excluded 158
Figure 4.17: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies 164
Figure 4.18: Risk of bias summary: review authors' judgements about each risk of bias item for each included study 166
Figure 5.1: HSE acute coronary syndrome model of care optimal reperfusion service protocol..... 178
Figure 5.2: PRISMA flow chart of included studies for RQ4 188
Figure 5.3: Meta-analysis of all-cause mortality (in-hospital/30 days) - RCTs 201
Figure 5.4: Forest plot of observational studies comparing all-cause mortality (in-hospital/30 days) by reperfusion strategy 201
Figure 5.5: Meta-analysis of re-infarction outcomes (in-hospital/30 days) – RCTs. 203
Figure 5.6: Meta-analysis of heart failure outcomes (in-hospital/30 days) – RCTs. 203
Figure 5.7: Subgroup analysis of heart failure outcomes by timepoints..... 204
Figure 5.8: Forest plot of RCTs comparing cardiac mortality outcomes between pharmacoinvasive and primary PCI groups (30 days) 205
Figure 5.9: Meta-analysis of total stroke outcomes (In-hospital/30 days) - RCTs .. 206
Figure 5.10: Meta-analysis of ischaemic stroke outcomes (In-hospital/30 days) - RCTs 207
Figure 5.11: Forest plot of RCTs comparing ICH outcomes (in-hospital/30 days) by reperfusion strategy 207
Figure 5.12: Forest plot of RCTs comparing total bleeding outcomes (in-hospital/30

days) by reperfusion strategy 208
Figure 5.13: Meta-analysis of major bleeding outcomes (in-hospital/30 days) - RCTs 209
Figure 5.14: Forest plot of observational studies comparing major bleeding outcomes (in-hospital) by reperfusion strategy..... 209
Figure 5.15: Forest plot of RCTs comparing minor bleeding outcomes (in-hospital/30 days) by reperfusion strategy 210
Figure 5.16: Forest plot of RCTs comparing composite outcomes (in-hospital/30 days) by reperfusion strategy 211
Figure 5.17: Forest plot of observational studies comparing composite outcomes (in-hospital/30 days) by reperfusion strategy 212
Figure 5.18: Forest plot of RCTs comparing rehospitalisation for cardiac causes (30 days) by reperfusion strategy 212
Figure 5.19: Risk of bias summary: review authors' judgements about each risk of bias item for each included RCT study, by outcome..... 214
Figure 5.20: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included observational studies, by outcome and by study..... 215

List of Abbreviations

ACCF	American College of Cardiology (Foundation)
ACS	acute coronary syndrome
ACHD	adult congenital heart disease
AGREE II	Appraisal of Guidelines for Research and Evaluation, Version Two
AHA	American Heart Association
AMA	American Medical Association
AMSTAR II	A MeaSurement Tool to Assess systematic Reviews, Version Two
ARI	absolute risk increase
ARR	absolute risk reduction
BR	baseline risk
BCIS	British Cardiovascular Intervention Society
CABG	coronary artery bypass graft
CASP	Critical Appraisal Skills Programme
Cath lab	catheterisation laboratory
CCG	clinical commissioning group
CCN	Cardiac Care Network of Ontario
CCU	coronary care unit
CI	confidence interval
CSANZ	Cardiac Society of Australia and New Zealand
CTO	chronic total occlusion
DBT	door-to-balloon time
DNT	door-to-needle time
DTB	door-to-balloon

EARLY-MYO	Early Routine Catheterisation After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction
ECG	electrocardiography
ED	emergency department
EMS	emergency medical services
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
FMC	first medical contact
HDI	Human Development Index
HIPE	Hospital In-Patient Enquiry
HR	hazard ratio
HSE	Health Service Executive
HTA	health technology assessment
GDP	gross domestic product
GPI	glycoprotein IIb/IIIa inhibitor
GRACIA-4	Grupo de Análisis de la Cardiopatía Isquémica Aguda 4
ICH	intra-cranial haemorrhage
ICU	intensive care unit
GISE	Italian Group of Hemodynamic Studies
GP	general practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIQA	Health Information and Quality Authority
HRB	Health Research Board

HRB-CICER	Health Research Board Collaboration in Ireland for Clinical Effectiveness Reviews
IABP	intra-aortic balloon counter pulsation pump
IHD	ischaemic heart disease
ICTRP	International Clinical Trials Registry Platform
IQR	inter-quartile range
ISRCTN	International Standard Randomised Controlled Trials Number
IVUS	intravascular ultrasound
KPI	key performance indicator
LMPCI	left main percutaneous coronary intervention
LMWH	low molecular weight heparin
MACE	major adverse cardiac events
MACCE	major adverse cardiac and cardiovascular events
mHealth	mobile health
MI	myocardial infarction
MOOSE	Meta-analysis Of Observation Studies in Epidemiology
MVPCI	multi-vessel percutaneous coronary intervention
NBT	needle-to-balloon time
NHS	National Health Service
NNTB	number needed to treat for an additional beneficial outcome
NNTH	number needed to treat for an additional harmful outcome
NSTEMI	non-ST-elevation myocardial infarction
NVVC	Netherlands Association of Cardiology
OCT	optical coherence tomography

OHCA	out of hospital cardiac arrest
OR	odds ratio
ORS	optimal reperfusion service
PCI	percutaneous coronary intervention
PICo	population, interest and context
PICOS	population, intervention, comparator, outcome and study design
PPCI	Primary percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
PTK	Polish Cardiac Society
QA	quality assurance
QALY	quality-adjusted life year
QI	quality indicator
RBT	randomisation-to-balloon time
RNT	randomisation-to-needle time
RCPI	Royal College of Physicians in Ireland
RCT	randomised controlled trial
RD	risk difference
RoB 2.0	Cochrane Risk of Bias version 2
RQ	review question
RR	relative risk

SAVR	surgical aortic valve replacement
UFH	unfractionated heparin
SCAD	stable coronary artery disease
SCAI	Society for Cardiovascular Angiography and Interventions
SCN	strategic clinical network
SICI	Italian Society of Invasive Cardiology
SOBT	symptom onset-to-balloon time
SONT	symptom onset-to-needle time
SORT	symptom onset-to-randomisation time
SOF	summary of findings
STEMI	ST-elevation myocardial infarction
STREAM	Strategic Reperfusion Early after Myocardial Infarction
STREAM 2	Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction
TAVI	transcatheter aortic valve implantation
TIA	transient ischaemic attack
UA	unstable angina

Executive Summary

Background to the request

The National Review of Specialist Cardiac Services (referred to in this report as the National Review), which convened in January 2018, is an independently chaired review of national clinical cardiac services in Ireland. It is designed to be underpinned by rigorous systematic reviews of evidence, robust data analysis of existing service provision, examination of relevant international good practice, and public and stakeholder consultation. The aim of the National Review is to achieve optimal patient outcomes at a population level with particular emphasis on the safety, quality and sustainability of the services that patients receive. The review will recommend the optimal configuration of a national adult specialist cardiac service in Ireland. Of particular interest to the National Review are regional specialist cardiac networks and network hospitals that are designated as general or comprehensive specialist cardiac centres based on the clinical needs of the population.

Description of the intervention

A specialist cardiac network can be defined as a network of designated specialist cardiac centres with stratified capability, supported by an ambulance service, which aims to meet patients' needs and improve the quality, safety and efficiency of care.

According to the Terms of Reference of the National Review, considered within scope of this evidence review were services for adults (18 years or older):

- presenting with cardiac problems such as acute coronary syndrome (ACS), heart failure and cardiac arrhythmias, or with adult congenital heart disease (ACHD) in need of acute and chronic (including cardiac rehabilitation) specialist cardiac services
- requiring access to cardiac diagnostics (both invasive and non-invasive), genetic testing and investigative services
- requiring access to cardiac syncope clinics, electrophysiology and catheterisation laboratories (cath labs).

Purpose of the evidence review

The main purpose of the evidence review is to synthesise evidence to inform the work of the National Review.

In light of discussions with the National Review Steering Group, it was clear that the management of ST-elevation myocardial infarction (STEMI) is one of the most time-

critical components of a specialist cardiac service. Treatment for STEMI involves rapid reperfusion through either fibrinolysis, involving the injection of fibrinolytic agents, or use of percutaneous coronary intervention (PCI), a procedure which widens the infarct–related artery through balloon angioplasty (and may or may not include stenting). PCI performed without prior administration of fibrinolytic therapy is known as primary PCI. Given the complexity of PCI procedures, the staffing, equipment and organisation of specialised interventional cardiology services capable of delivering PCI (and particularly primary PCI) will likely also fulfil the requirements for other complex and acute cardiac conditions. Therefore, it was agreed in consultation with the National Review Steering Group to use PCI as the exemplar procedure, with the evidence around the configuration of PCI services as the essential component to inform the design of the 'hub' of a 'hub and spoke' model.

Therefore, the three main objectives of this evidence review were to:

- identify and describe existing models of specialist cardiac networks, focusing primarily on countries with the most relevance to the Irish healthcare system
- identify international best practice for centres providing PCI and to examine the evidence underpinning these criteria
- identify evidence on the safety and effectiveness of strategies for managing STEMI including primary PCI and pharmacoinvasive approaches in centres without PCI-capability.

Overall methodological approach

This research was conducted in accordance with the Health Information and Quality Authority's (HIQA) guidelines for evaluating the clinical effectiveness of health technologies in Ireland. Four review questions were developed to address the objectives stated above:

RQ1. What international models for specialist cardiac networks exist that might be applicable to the Irish healthcare system?

RQ2. What organisational and service criteria do national or international guidelines, policy statements, recommendations and standards specify for centres providing PCI for cardiac conditions in adults?

RQ3. What is the relationship between procedure volume and patient outcomes for PCI?

RQ4. What is the safety and effectiveness of a pharmacoinvasive strategy compared with primary PCI for adults diagnosed with STEMI?

Due to the exploratory and broad nature of the first review question (RQ1), a traditional systematic review methodology was not appropriate and therefore this question followed a scoping review methodology. Review questions two (RQ2), three (RQ3) and four (RQ4) followed traditional systematic review methodologies. A meta-analysis was also conducted for RQ3 and RQ4 as the data were judged to be suitable for this analytical approach.

RQ1: International models of specialist cardiac networks

A scoping review was undertaken to identify and describe existing models of specialist cardiac networks, primarily focusing on countries most relevant to the Irish healthcare system. Eighty-two specialist cardiac networks located across 21 countries were identified. Of the 82 identified networks, 75 were ACS-related (52 of which were STEMI networks), and seven were non ACS-related. 'Hub and spoke' models featured prominently in ACS-related networks. Three networks, located in Emilia-Romagna, Catalonia and England, were identified as examples which could potentially provide information relevant to the Irish healthcare system. A detailed description of these networks was provided.

Key performance indicators (KPIs) commonly monitored across the 82 networks were mortality/survival, procedural complications, time-to-treatment, healthcare utilisation, medications, neurological function and reperfusion strategy use. Not all PCI centres in the identified networks offered a 24/7 service; some provided part-time services. At least 55 of the 75 ACS-related networks provided a 24/7 PCI service in at least one hospital within the network. The maximum distance between a PCI centre and a non-PCI centre within a network ranged from 11km to 430km, with an average maximum distance of 113km. The population served per 24/7 PCI centre ranged from 120,000 to 2.5 million inhabitants, with the majority of identified networks (72%) sitting within the 'optimal' range of 300,000 to 1.1 million inhabitants. It was estimated that at a national level in Ireland, the population served per 24/7 PCI centre was approximately 920,000 inhabitants.

Although there was limited international evidence regarding the structure and organisation of networks for other cardiac conditions, it is plausible that they may fall in line with a 'hub and spoke' model integrated with STEMI 'hub and spoke' networks. In particular, it has been suggested that heart failure networks take a similar structure, however, unlike STEMI networks; proposed 'hub and spoke' models for heart failure are more complex as they extend beyond specialist networks into the community, and hence primary care involvement is critical to the establishment of such networks.

RQ2: Organisational and service specification recommendations for centres providing PCI

A systematic review of national and international guidelines, policy statements, recommendations and standards (referred to in this document using the umbrella term 'guidance documents') published since 2008, was undertaken to collate organisational and service specification recommendations for PCI. From 7,988 citations identified, 22 guidance documents were included: 10 from Europe, seven from North America and five from the Asia-Pacific region. The Appraisal of Guidelines for Research and Evaluation Two (AGREE II) tool was used to appraise the quality and reporting of included guidance documents. Overall the guidance documents scored well in terms of stating the scope and purpose of the document and clearly presenting the recommendations, but scored poorly in the rigour of development domain (as it was often unclear what evidence underpinned the recommendations). Most of the guidance documents made no conflict of interest or funding statement.

Sixteen of the 22 guidance documents made recommendations on institutional facilities for PCI centres, with some listing additional requirements for centres providing primary PCI. Nineteen guidance documents made recommendations on institutional volume with the minimum recommended number of primary and total PCI procedures performed per centre ranging from 36 to 150 procedures per year and from 200 to 600 procedures per year, respectively. Seventeen guidance documents made recommendations on operator volume with the minimum recommended number of primary and total PCI procedures performed by an operator ranging from 11 to 30 and from 50 to 150 procedures per year, respectively.

Eleven guidance documents made recommendations on surgical cover, stating that both elective and primary PCI may be considered in hospitals without on-site cardiac surgery provided that there are clear and documented systems in place for the urgent transfer of patients to a facility with cardiovascular surgical support within recommended timeframes. Twelve guidance documents made recommendations on staffing levels, which varied considerably between guidance documents and depending on the jurisdiction. They appeared to be based on local policy rather than being underpinned by any empirical research. Depending on the guidance document, at least one interventional cardiologist and one to four additional staff members with specific roles (such as nurses, certified technologists, assistant physicians, radiographers, physiologists, laboratory technicians or co-ordinators) were recommended per PCI procedure. Between two and four interventional cardiologists were recommended per primary PCI centre depending on the number of rooms and whether the service was provided 24/7, though it has been suggested that a sustainable rota for a primary PCI centre should comprise a minimum of six

and ideally 10 interventional cardiologists, facilitated by rostering of staff between hospitals within a network. Considerations included the minimum number of procedures an operator needs to complete to maintain competence and staff rest times, which are likely informed by working time directives and usual staff contractual arrangements. Furthermore, staffing rosters may be organised to minimise the time spent by individual staff members in cardiac catheterisation laboratories given the significant occupational health risks associated with long-term ionising radiation exposure.

Fifteen guidance documents made recommendations on time or distance to treatment. The most often quoted was a door-to-balloon time of less than 90 minutes and the use of fibrinolysis instead of primary PCI if transport time exceeds 90 minutes or 120 minutes, depending on the guidance document. Nineteen guidance documents made recommendations on monitoring of standards, providing multiple KPIs and recommending the creation of local databases to allow for the recording and monitoring of procedures and outcomes and the use of national or regional registries to allow benchmarking and tracking of complications.

RQ3: The relationship between procedure volume and patient outcomes for PCI

A systematic review and meta-analysis was undertaken to examine the relationship between PCI procedural volume and patient outcomes, given the unclear evidence base for recommendations identified in RQ2 and in light of advances in interventional cardiology. Of 1,154 unique records retrieved, 22 studies conducted in eight countries were included. In total, 6,432,265 patients or procedures were included across the 22 studies. All included studies were observational in nature. For each study, outcomes for the highest-volume providers/hospitals were compared with those of their lowest-volume counterparts, although the number of groups per study and how they were assigned (pre-specified (for example, tertiles and quartiles) or data-driven) differed substantially.

No significant association was found between total PCI hospital volume and mortality (odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.69-1.03). That is, for total PCI procedures, no difference in mortality was found between high and low volume hospitals. The relationship between procedure numbers and outcomes appears be lessening over time as an apparent temporal trend from significant to non-significant was observed. For primary PCI procedures, the pooled effect estimate was found to be significantly in favour of high-volume hospitals. That is for primary PCI procedures, high-volume hospitals were associated with a 23% reduction in the odds (OR: 0.77, 95% CI: 0.62-0.94) of post-operative mortality. At an individual operator level, the pooled effect estimate was also found to be significantly in favour of high-

volume operators for total PCI procedures (OR: 0.77, 95% CI: 0.63-0.94). However, all three meta-analyses had considerable levels of heterogeneity (I^2 = 86%, 93% and 78%, respectively), hence caution is required when interpreting these pooled effect estimates. Only two studies investigated the relationship between primary PCI at the operator level and mortality, and these studies reported conflicting findings.

Definitions of high and low volume varied widely between studies, and hence it was not possible to calculate a minimum volume threshold. In two studies that evaluated long-term mortality outcomes, it would appear that the volume-outcome relationship attenuated over time in these studies. The volume-outcome relationship within specific patient subpopulations was inconsistent. The association between procedural volume and PCI complications was also inconsistent. There appeared to be a consistently significant relationship between procedural volume and healthcare utilisation or process outcomes (such as hospital length of stay or time-to-treatment), in favour of high-volume operators and hospitals. However one study found that very high-volume hospitals and operators were more likely to perform a higher proportion of inappropriate PCIs (as defined using US Appropriate Use Criteria).

Methodological quality was assessed using a modified version of the Critical Appraisal Skills Programme (CASP) tool for cohort studies. Eight of the 22 studies were judged to have an overall low risk of bias, nine an unclear risk of bias and five a high risk of bias.

Importantly, the certainty of the evidence was assessed as 'very low' (using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach) due to the observational nature of included studies, a high or unclear risk of bias across many included studies, the considerable levels of heterogeneity and some concerns regarding the imprecision of results. Consequently, these results should be viewed with caution.

RQ4: Pharmacoinvasive strategy versus Primary PCI for STEMI

A systematic review and meta-analysis was undertaken to compare the safety and effectiveness of a pharmacoinvasive strategy with primary PCI for adults diagnosed with STEMI. Primary PCI is generally considered the gold standard for STEMI treatment; however, this is contingent on the procedure being conducted in a timely manner. A pharmacoinvasive strategy is generally recommended as a suitable alternative if delays are expected in getting to a PCI-capable centre. A pharmacoinvasive strategy is defined as fibrinolysis followed by routine rapid transfer to a PCI-capable centre; immediate PCI (that is, rescue PCI) only for

patients with failed fibrinolysis; and routine angiography, with or without PCI, within 3–24 hours after successful fibrinolysis.

Of 1,825 unique records retrieved, 14 studies (five randomised controlled trials (RCTs) and nine observational studies) conducted in 20 countries were included. In total, 41,118 patients were included across all 14 studies (2,977 from RCTs and 38,141 from the observational studies). The Cochrane Risk of Bias version 2.0 tool (RoB 2.0) for RCTs was used to assess bias in the RCTs focusing on mortality and bleeding outcomes. The overall risk of bias was judged as 'some concerns' for four outcome-level assessments across three RCTs and 'high risk' for the remaining six outcome-level assessments across four RCTs. Using the CASP quality appraisal tool for cohort studies, three observational studies were judged to have an overall low risk of bias, three an unclear risk of bias and three a high risk of bias.

The RCT data relate to patients in the early phase of STEMI at diagnosis (ranging from less than three hours to less than 12 hours from symptom onset) for whom an initial PCI-related delay is expected (60-90 minute delay before cath lab arrival). The observational data reflect 'real-world' practice where one patient cohort undergoes primary PCI and another cohort undergoes a pharmacoinvasive strategy based on clinical, geographical and logistical reasons. This review found that, where initial PCI-related delays are expected, a pharmacoinvasive strategy has comparable effectiveness to primary PCI. Furthermore, evidence suggests that within this context (that is, restricted to patients with initial expected delays in accessing PCI), timely treatment with a pharmacoinvasive strategy may be more effective than delayed primary PCI where the time difference exceeds 80 minutes.

The review also found evidence of some safety concerns with a pharmacoinvasive strategy. Specifically, relative to primary PCI there was an increased risk of minor bleeding (driving the observed increased risk of total bleeding events) and intracranial haemorrhage (ICH) (driving the observed increased risk of total stroke events), albeit noting that these latter events were uncommon. Meta-analysis of in-hospital or 30-day follow-up data from four RCTs found that patients randomised to a pharmacoinvasive strategy had over a four-fold higher odds of having a stroke compared with patients randomised to primary PCI (OR: 4.26, 95% CI; 1.52–14.16). When calculated as the number needed to treat for one additional harmful outcome (NNTH), this would suggest that for every 70 patients treated with a pharmacoinvasive strategy instead of primary PCI, one additional stroke may occur. However, there is a substantial level of uncertainty around this point estimate (NNTH: 70, 95% CI: 16–433). 'Real-world' observational evidence included in this review suggested that after adjusting for important confounders, no significant differences were observed between the two strategies in terms of all-cause mortality, total bleeding or major bleeding; however, the relationships between

reperfusion strategy and ICH or stroke were not evaluated in these observational studies. Ongoing research is investigating the use of half-dose tenecteplase in older patients as a means of mitigating the safety concerns associated with pharmacoinvasive strategies.

The certainty of the evidence for all outcomes was rated as 'low' to 'very low' due to the limited number and the small sample size of some of the included studies, the relatively low frequency of some of the endpoints under investigation, some concerns regarding the risk of bias and the observational nature of some of the studies. Furthermore, there are limited data to determine the pooled effect estimate and absolute effect measures for several of the outcomes under investigation. Of note, the data are limited to patients presenting within 12 hours (and sometimes three hours) of STEMI onset.

Discussion

A scoping review of international specialist cardiac networks, and in particular STEMI networks, found that they were generally organised as 'hub and spoke' models, with more specialised services centralised to high-volume 'hubs', supported by referring 'spoke' hospitals on the periphery of the system and a coordinated ambulance system. Less international evidence was found to support any specific organisation of heart failure, cardiac arrhythmia or ACHD networks, although these could align with STEMI networks. Clear governance structures also appeared to be important for sustainability and development of specialist cardiac networks. From an organisational standpoint, the ACS programme operated by the Health Service Executive (HSE) appears to be in alignment with international networks.

The organisation and service specifications for PCI centres, as the 'hub' of the cardiac network, were systematically collated and the underpinning evidence was examined. Although there were common themes that a number of guidance documents agreed on, there were also some clear areas of divergence, which may be related to the differences in healthcare systems of the various countries and regions. Continuous monitoring of standards with adequate quality assurance systems were recommended by most guidance documents to ensure safe, effective and high-quality care. Minimum-volume threshold recommendations in particular were quite variable, arbitrary and of uncertain evidence. Moreover, for the majority of included guidance documents, the evidence base underpinning the recommendations and the methodology for formulating the recommendations was unclear. Due to the variability of these thresholds and uncertainty of the underpinning evidence, procedure volumes in isolation should not be considered an indication of quality care, and the performance of a PCI centre or operator should be considered in the context of other factors, including other KPIs. Although guidance

documents varied with regards to staffing recommendations, careful consideration must be given to the number, location and resourcing of centres. This is to ensure a balance can be achieved between accessibility and the provision of safe, efficient PCI services that, particularly in the case of low-volume 24/7 PCI centres, have sufficient volume to allow staff maintain competence and to facilitate the sustainable recruitment and retention of adequate numbers of appropriately qualified staff with sufficient expertise in order to meet international best practice.

A volume-outcome relationship was previously found to exist for PCI. In light of significant advances in interventional cardiology, this relationship was re-examined to determine whether high-volume PCI hospitals or operators are still associated with better patient outcomes compared with their low-volume counterparts. The majority of evidence identified in the systematic review related to the impact of volume on mortality. Findings from the meta-analysis suggest that a volume-outcome relationship may still exist in favour of high-volume hospitals for primary PCI procedures and in favour of high-volume operators for total PCI procedures. No such association was found between total PCI hospital volume and mortality, with a clear temporal trend from significant to non-significant observed. That is, while studies based on earlier data observed an association between hospital PCI volume and mortality, over time this relationship has waned. This is possibly due to technical improvements in how the procedure is carried out and better standardisation of care in hospitals. These results should be viewed with caution as the certainty of the evidence was judged to be 'very low' due to the considerable levels of heterogeneity, concerns regarding the risk of bias of included studies, and variations as to how high and low volume were defined. Typically, studies compared the outcomes from the highest volume operator (or hospital) with that of the lowest. It was not possible to determine a specific minimum-volume threshold. Of note, none of the current Irish designated PCI centres met the definition of low volume used in the majority of the studies included in this review. The relationship between procedural volume and other outcomes was mixed, and although there appeared to be a consistently significant association between higher procedural volume and improved healthcare utilisation or process outcomes, ongoing research of this relationship is required.

While acknowledging uncertainty around a PCI volume-outcome relationship, there may be concerns regarding the sustainability of a low-volume PCI centre given that a number of international guidelines specifically recommend that primary PCI centres should provide a 24/7 service and that they should have a second cath lab on-site. While there was heterogeneity between guidelines and networks identified in this review, there are likely minimum infrastructure and staffing requirements to provide safe and sustainable 24/7 services at PCI centres that will pertain irrespective of the volume of procedures provided. Alternatives to investing in new low-volume PCI centres include consideration of the other steps in the pathway from symptom onset

to reperfusion such as awareness raising regarding STEMI symptoms and management, additional resourcing of prehospital systems of care and or improved interhospital transfer to address specific issues in geographically remote regions. The goal is to maximise patient outcomes while ensuring an efficient and sustainable use of resources; however, a determination of the economic implications of alternative approaches was beyond the scope of this project.

The review found evidence that a pharmacoinvasive approach is a suitable alternative to primary PCI for STEMI patients who are unable to access PCI in a timely manner. Furthermore, evidence was found suggesting, that within this context (that is, restricted to patients with initial expected delays in accessing PCI), a pharmacoinvasive strategy may be associated with better patient outcomes where the time difference exceeds 80 minutes. The certainty of the evidence was rated 'low' to 'very low' due to the limited number and the small sample size of some of the included studies, the relatively low frequency of some of the endpoints under investigation, some concerns regarding the risk of bias and the observational nature of some of the studies. This means that the findings should be interpreted with caution, as the true effect could be markedly different (better or worse) than that estimated. Of note the data are limited to patients whose symptom onset does not exceed 12 hours, so the findings do not apply to evolved STEMIs. Evidence of possible safety concerns with a pharmacoinvasive strategy were also found. These concerns specifically relate to an increased risk of minor bleeding (driving an increased risk of total bleeding events) and ICH (driving an increased risk of total stroke events); however, these latter adverse events are uncommon. Implementation of appropriate care pathways for patients who experience these complications, including use of alternative dosing strategies in elderly patients, may mitigate these risks. As with the effectiveness data, the safety findings must be interpreted with caution as the certainty of the evidence was rated as 'low' to 'very low'. The findings from this review question which is based on current cardiology practice supports the current optimal reperfusion service (ORS) for Ireland. The ORS recommends that patients should be transferred for primary PCI if transport to a primary PCI centre is possible within 90 minutes of STEMI diagnosis; otherwise a pharmacoinvasive strategy is recommended.

The robustness of this evidence review is its key strength generating findings that are strongly rooted in evidence, are relevant and important for informing national health policy. The main limitation of this evidence review is that many of the included studies had methodological issues and or were observational in nature. Furthermore, the overall certainty of evidence was 'low' or 'very low' in the two review questions where GRADE was applied. It is important that policy makers are aware of the limitations of the evidence base.

Although most of the evidence presented in this review focuses on STEMI networks and PCI centres, it is likely that any 'hub' that can provide PCI care will also be capable of providing care for a range of other cardiac conditions. Based on a limited number of non-ACS networks identified in RQ1, it is possible that other cardiac services such as those for heart failure could be organised using a 'hub and spoke' model.

In the event that a specialist adult cardiac network is established in Ireland that provides care across the range of cardiac conditions identified for inclusion by the National Review's Steering Group, international best practice would suggest that an investment in systems for monitoring performance would be an essential part of the implementation plan. Any quality assurance programme for a cardiac network should allow for the identification and collection of appropriate regional data, benchmarking against agreed national standards, and a feedback mechanism that would allow for improvements in practice. Careful consideration should also be given to other national strategies and policies, and in particular any requirements for common support services.

Summary of key outcomes from evidence reviews

- Specialist cardiac networks, particularly STEMI networks, are commonly organised into regional 'hub and spoke' networks.
- The organisation of the national Irish ACS programme, which was implemented in 2013, appears to be in alignment with international models.
- Organisational and service specification recommendations for centres providing PCI varied substantially among guidance documents, particularly around recommendations for procedure volumes and staffing, but agreed on other areas such as the need for monitoring of standards.
- Although a PCI volume-outcome relationship may exist under certain circumstances in favour of high-volume hospitals and operators, it would appear that volume should not be the only standard used to define an acceptable PCI service.
- The certainty of the evidence for a volume-outcome relationship is 'very low' due to the considerable levels of heterogeneity, concerns regarding the risk of bias of included studies and variations in how high- and low-volume were defined.
- It was not possible to determine with any degree of certainty a specific minimum-volume threshold.
- A pharmacoinvasive strategy is a suitable alternative to primary PCI for STEMI

patients who are unable to access PCI in a timely manner, and for whom symptom onset does not exceed 12 hours.

- Although rare, there are some safety concerns with regards an increased risk of bleeds with a pharmacoinvasive strategy, specifically regarding minor bleeding (driving an increased risk of total bleeding events) and ICH (driving an increased risk of total stroke events). Ongoing research is investigating the use of half-dose tenecteplase in older patients as a means of mitigating these safety concerns.
- The certainty of the evidence for the alternative reperfusion strategies for STEMI is 'low' to 'very low' due to the limited number and the small sample size of some of the included studies, the relatively low frequency of some of the endpoints under investigation, some concerns regarding the risk of bias and the observational nature of some of the studies.

The National Review of Specialist Cardiac Services, aims to achieve optimal patient outcomes at a population level with particular emphasis on the safety, quality and sustainability of the services that patients receive. It will recommend the optimal configuration of a national adult specialist cardiac service in Ireland. The National Review was designed so that it would be underpinned by rigorous systematic reviews of evidence, robust data analysis of existing service provision, examination of relevant international good practice, and public and stakeholder consultation. Regional specialist cardiac networks and network hospitals that are designated as general or comprehensive specialist cardiac centres based on the clinical needs of the population were identified as being of particular interest. In consultation with the National Review Steering Group, it was agreed to use PCI as the exemplar procedure with the evidence around the configuration of PCI services used as an essential component to inform the design of the 'hub' of a 'hub and spoke' model in this evidence review. PCI was selected as it was identified that the management of ST-elevation myocardial infarction (STEMI) is one of the most time-critical components of a specialist cardiac service. Given the complexity of PCI procedures, the staffing, equipment and organisation of specialised interventional cardiology services capable of delivering PCI (and particularly primary PCI) will likely also fulfil the requirements for other complex and acute cardiac conditions. Therefore, while this evidence summary only looked at PCI services, it is likely that the findings are relevant to the configuration of other specialist cardiac services.

While guidance documents may differ with regards to staffing recommendations for specialist centres, careful consideration must be given to the number, location and resourcing of such centres. This is to ensure a balance can be achieved between accessibility and the provision of safe, efficient services that, particularly in the case of low-volume specialist centres, have sufficient volume to allow staff maintain

competence and to facilitate the sustainable recruitment and retention of adequate numbers of appropriately qualified staff with sufficient expertise in order to meet international best practice. Alternatives to investing in new low-volume specialist centres include consideration of the other steps in the patient care pathway from awareness raising regarding symptoms and their management, additional resourcing of prehospital systems of care and or improved interhospital transfer to address specific issues in geographically remote regions. However, a determination of the economic implications of alternative approaches was beyond the scope of this project. When recommending the optimal configuration for specialist cardiac services in Ireland, consideration should be given to other national strategies and policies, and in particular any requirements for common support services. Investment in systems for monitoring performance should be an essential part of any implementation plan. A quality assurance programme for a cardiac network should allow for the identification and collection of appropriate regional data, benchmarking against agreed national standards, a feedback mechanism that would allow for improvements in practice, and a means to address some of the uncertainty due to limited data.

Plain English Summary

A review of the evidence relating to how specialist cardiac services for adults are organised in other countries was carried out. These specialist cardiac services provide care for:

- heart attacks
- heart failure
- irregular heart beats
- congenital heart disease (structural heart problems that people are born with).

These specialist cardiac services also provide patients with access to tests and procedures for these heart conditions. These services tend to be organised into groups of hospitals called networks. This review of the evidence was carried out to help the National Review of Specialist Cardiac Services Steering Group make better informed decisions about the organisation of specialist cardiac services for adults in Ireland. The goal of specialist cardiac services is to provide a safe, sustainable, quality-assured service that provides the best possible outcomes for patients.

In this review of the evidence, four separate review questions were addressed. The first question looked at how countries similar to Ireland organise their specialist cardiac services. It found a variety of specialist cardiac networks, although most focused on the urgent treatment of patients presenting with major heart attacks. These networks were most commonly set up in the following way: a small number of hospitals (known as PCI centres) treat heart attacks, smaller surrounding hospitals transfer their patients to the PCI centres and the emergency/ambulance services will bypass all of the smaller surrounding hospitals and go directly to the PCI centres for patients experiencing heart attacks. This is known as a 'hub and spoke' model.

The second question looked to see what guidance documents, from Ireland or other countries, consider to be best practice for patients presenting with major heart attacks. These are known as STEMIs (ST-elevation myocardial infarctions) and they are caused by a blockage in the arteries supplying blood to the heart muscle. They are considered a medical emergency and are treated urgently by using either a clot-busting drug (thrombolysis) or by inserting a guide wire into the artery and opening the vessel using a balloon to allow the blood to flow to the heart muscle again. This is known as a primary percutaneous coronary intervention (PCI), and is done in a hospital that has an emergency catheterisation laboratory (cath lab). For this question we found that there was a high level of difference between guidance documents in how they defined best practice for PCI centres, especially around recommendations for the minimum number of procedures to be performed by hospitals or operators and also on the staffing requirements for PCI centres. The

documents agreed on other areas, such as the need to establish standards for care and to audit and monitor centres to assess how they are performing and to see where improvements need to be made.

The third question asked whether there was a link between the number of PCI procedures performed by a hospital or by a specific operator (the doctor who performs the procedure) and patient outcomes following the procedure. We found that in certain circumstances, hospitals and operators who perform a higher number of PCI procedures each year have fewer patient deaths after the procedure than hospitals or operators who perform fewer procedures. However, in other circumstances, no differences in the number of patient deaths were found. The effect of procedure numbers on patient deaths seems to be lessening over time. This is possibly due to technical improvements in how the procedure is carried out and better standardisation of care in hospitals. There were a lot of differences between the studies that investigated this effect, so this finding should be viewed carefully. The studies differed in how they defined high- volume and low- volume hospitals and operators. Some used a minimum number of procedures that a hospital or operator carries out in a given year to define what a low-volume hospital or operator is; however, this number differed between studies. Based on the evidence we found for this question, it was not possible to determine a specific minimum number of procedures per year that should be performed by a hospital or an individual operator to achieve better outcomes. The effect of procedure numbers on other patient outcomes, such as bleeding, differed between studies. For these reasons, it is important that the quality of care provided by a hospital or operator is not decided simply by the number of PCI procedures performed.

The fourth question asked whether the two different approaches for managing major heart attacks (STEMIs) have similar outcomes. The first approach is called a pharmacoinvasive strategy. This involves giving the patient a clot-busting drug as first-line treatment before transferring them to a PCI-capable centre. If treatment with the clot-busting drug is unsuccessful, the patient would proceed to immediate PCI. All other patients are sent to the cath lab for angiography between a minimum of three hours, but no more than 24 hours after the clot-busting drug to examine the extent to which the blockage has cleared. If only partially cleared, the doctor proceeds to do a PCI. The second approach is primary PCI. Instead of giving any clot-busting drugs, the patient is immediately transferred to the nearest cath lab and PCI is done straight away. This approach is currently considered the best treatment option for patients with major heart attacks; however, guidelines recommend that the PCI should be done within two hours of the diagnosis. For this question we found that for patients who present early with heart attack symptoms, but who cannot get to a primary PCI centre quickly, both primary PCI and a pharmacoinvasive strategy have similar outcomes. The number of deaths, repeat

heart attacks, heart failure and shock were similar between groups. As clot-busting therapy can be started in a wider range of settings than primary PCI, it may allow for faster treatment. When looking only at patients that could not get to the cath lab for at least one hour, we found that outcomes may even be better with a pharmacoinvasive strategy delivered sooner, than primary PCI that is greatly delayed. However, while fairly uncommon, there are some safety concerns as more cases of bleeding and stroke occurred in the pharmacoinvasive group. For every 70 patients treated with a pharmacoinvasive strategy instead of primary PCI, one additional stroke may occur. However, this estimate is very uncertain, and there could be as many as one additional stroke per 16 patients treated or as few as one additional stroke per 433 patients. Continued research is needed to identify how to reduce the risk of these events in at-risk patients. The current optimal reperfusion service (ORS) for Ireland recommends that patients should be transferred for primary PCI if transport to a primary PCI centre is possible within 90 minutes of STEMI diagnosis; otherwise a pharmacoinvasive strategy is recommended. Our review, based on current evidence supports this practice of having both options available for STEMI patients. It is also consistent with the approach taken by other countries, where the treatment chosen depends on where you live and how long it takes to get to the hospital.

This review of the evidence was carried out to support the National Review of Specialist Cardiac Services Steering Group make informed decisions about how best to organise specialist cardiac services for adults in Ireland. These specialist cardiac services cater for a diverse group of patients with a wide range of heart conditions and differing needs. Such services are often organised in a 'hub and spoke' model where very complex or acute care is provided in a small number of very specialised centres 'hubs' supported by other less specialised centres that can provide more of the patient's routine care closer to their homes. PCI for the management of STEMI is an example of the type of procedure that is only carried out in a 'hub'. Standards and requirements for a PCI centre are likely also to be relevant for other procedures or conditions that should only be managed in specialised centres.

Guidance documents made different recommendations about the minimum number of patients a specialist centre should treat and about the number of staff and type of the resouces they require. Looking across all the evidence, it is clear that careful consideration must be given to the number, location and resourcing of such centres. This is to ensure a balance can be achieved between making it quicker and easier for patients to access care and ensuring that the care that is provided in each centre is safe and efficient. This is particularly the case for specialist centres that only treat a small number of complex cases each year. These centres need to treat enough patients to allow staff maintain competence and to ensure that they can attract and retain staff that are sufficiently qualified and experienced to meet international best

practice standards. Alternatives to investing in new low-volume specialist centres include consideration of the other steps in the patient care pathway. This could include raising awareness for patients and the public about the symptoms of certain heart complications and how they should be managed. It could include additional resources for prehospital systems of care or improved interhospital transfer to ensure timely care for patients living in geographically remote areas. However, a determination of the economic implications of alternative approaches was beyond the scope of this project.

No matter which way the specialist cardiac services in Ireland are organised, a key requirement will be to invest in systems for gathering data and monitoring performance. Having a quality assurance programme in place would allow the care in each centre to be bench marked against agreed national standards, against each other and against international centres. It would highlight where improvements in practice are needed and provide a means to address some of the uncertainty due to limited data.

1 Introduction

1.1 Background to the request

The National Review of Specialist Cardiac Services (referred to in this report as the National Review), which convened in January 2018, is an independently chaired review of national clinical cardiac services in Ireland. It is designed to be underpinned by rigorous systematic reviews of evidence, robust data analysis of existing service provision, examination of relevant international good practice, and public and stakeholder consultation. The aim of the National Review is to achieve optimal patient outcomes at a population level with particular emphasis on the safety, quality and sustainability of the services that patients receive. The review will recommend the optimal configuration of a national adult specialist cardiac service in Ireland. Of particular interest to the National Review are regional specialist cardiac networks and network hospitals that are designated as general or comprehensive, specialist cardiac centres based on the clinical needs of the population.[1]

Clinical networks are increasingly being established in a number of clinical disciplines, such as trauma[2, 3] and stroke,[4, 5] as a strategy to drive improvements in patient care by integrating services and collaborating across disciplines. Many countries are investing in clinical networks;[6] however, it is not yet clear whether there are differences in how these networks are configured.

The reconfiguration of cardiovascular healthcare delivery has largely been driven by evidence of a relationship between hospital and or operator procedure volumes and patient outcomes.[7-10] Consequently, international guidelines have recommended hospital-level minimum volume standards for selected procedures, including percutaneous coronary interventions (PCI), with the aim of improving patient outcomes.[11, 12] However, using volume as an indicator of quality and competency, particularly for PCI, has been called into question due to significant technological advances and improvements in perioperative management in recent years.[13] Furthermore, reconfiguring hospital networks can result in reduced access to services, as lower-volume centres serving rural areas may be closed.[14]

Given international developments in the configuration of clinical networks, the evolving evidence regarding the relationship between procedure volume and patient outcomes and the uncertainty regarding how best to manage STEMI in regions without PCI capability, the configuration of specialist cardiac services that would best meet the needs of the Irish population is yet to be determined.

Preliminary evidence research questions were developed in line with the terms of reference of the National Review by its Steering Group. These were sent to the Evidence for Policy team for further refinement in October 2018. Following scoping

of the topic, the Evidence for Policy Team drafted four potential evidence review questions which they presented to the Steering Group for debate and discussion on 12 November 2018. At this meeting, three of the four evidence review questions were prioritised; these are outlined in section 1.3 below. A protocol for the Evidence Review of Specialist Cardiac Services based on these three evidence review questions was subsequently finalised and agreed upon by the Chair of the National Review, the Head of Clinical Effectiveness and the Director of Health Technology Assessment, in January 2019. The findings of these three evidence review questions were presented to the Steering Group for discussion on 14 June 2019. In July 2019, the Evidence for Policy team was asked to undertake a systematic review to answer an additional review question. This fourth question created a third objective (outlined in section 1.3 below), which examines the current evidence underpinning pharmacoinvasive strategies that are the basis for the current management of STEMI outside of PCI-capable centres.

1.2 Description of the intervention

Clinical networks can be defined in different ways and a number of models have been proposed for use in a range of clinical disciplines.[6, 15] A clinical specialist cardiac network can be defined as a network of designated, specialist cardiac centres with stratified capability, supported by an ambulance service, which aims to meet patients' needs and improve the quality, safety and efficiency of care.

The following definitions of clinical networks will be used in this review and were agreed with the National Review's Steering Group:

- Managed clinical networks — groups of clinicians who deliver services across the boundaries between healthcare professions and the different sectors of the health system.

- Network models of cardiac care with a hierarchical structure — networks made up of healthcare organisations, as well as the individuals within them, with an overarching administrative structure and with a focus on integration and coordination of clinical services; also known as integrated service delivery.

According to the Terms of Reference of the National Review, considered within scope of this evidence review were services for adults (18 years or older):

- presenting with cardiac problems such as acute coronary syndrome (ACS), heart failure and cardiac arrhythmias, or with adult congenital heart disease (ACHD) in need of acute and chronic (including cardiac rehabilitation) specialist cardiac services

- requiring access to cardiac diagnostics (both invasive and non-invasive), genetic testing and investigative services
- requiring access to cardiac syncope clinics, electrophysiology and catheterisation laboratories.

In light of discussions with the National Review Steering group, it was clear that the management of ST-elevation myocardial infarction (STEMI) is one of the most time-critical components of a specialist cardiac service and that evidence to inform the configuration of percutaneous coronary intervention (PCI) services is considered essential to inform deliberations for the National Review. The staffing, equipment and organisation of specialised interventional cardiology services capable of delivering PCI (and particularly primary PCI) will likely also fulfil the requirements for other complex and acute cardiac conditions. Therefore, in consultation with the Steering Group, it was agreed to use PCI as the exemplar procedure to develop the evidence to inform the design of the 'hub' of a 'hub and spoke' network model.

1.3 Purpose of the evidence review

The main purpose of the evidence review was to synthesise evidence to inform the work of the National Review of Specialist Cardiac Services, which aims to recommend the best configuration for a national adult specialist cardiac service with population-based regional specialist cardiac networks and network hospitals.

The three main objectives therefore identified for the evidence review were to:

1. Identify and describe existing models of specialist cardiac clinical networks, focusing primarily on countries with the most relevance to the Irish healthcare system.
2. Identify international best practice for centres providing PCI, and to examine the evidence underpinning these criteria.
3. To identify evidence on the safety and effectiveness of strategies for managing STEMI, including primary PCI and pharmacoinvasive approaches in centres without PCI-capability.

The following four review questions are addressed by this evidence review:

1. Review question one (RQ1): What international models for specialist cardiac networks exist that might be applicable to the Irish healthcare system?
2. Review question two (RQ2): What organisational and service specifications do national or international guidance documents recommend for centres providing

PCI for cardiac conditions in adults?

3. Review question three (RQ3): What is the relationship between procedure volume and patient outcomes for PCI?

4. Review question four (RQ4): What is the safety and effectiveness of a pharmacoinvasive strategy compared with primary PCI for adults diagnosed with STEMI?

1.4 Overall methodological approach for the evidence review

Due to the exploratory and broad nature of RQ1, a traditional systematic review methodology was not appropriate and therefore this question followed a scoping review methodology.[16, 17] Scoping reviews are often used for the following purposes:[16]

- to identify the types of available evidence in a given field
- to clarify key concepts or definitions in the literature
- to examine how research is conducted on a certain topic
- to identify key characteristics or factors related to a certain concept
- as a precursor to a systematic review
- to identify and analyse knowledge gaps.

Review questions two, three and four (RQ2, RQ3 and RQ4) were registered with the PROSPERO database of prospectively registered systematic reviews (CRD42019127622, CRD42019125288 and CRD42019148276, respectively). RQ2, RQ3 and RQ4 adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria,[18] while RQ1 adhered to the PRISMA extension for scoping reviews (PRISMA-ScR).[19] In addition, RQ2 used some of the key stages of the ADAPTE methodology, specifically with regard to the assessment of included guidelines;[20] RQ3 adhered to Meta-analysis Of Observation Studies in Epidemiology (MOOSE) criteria;[21] and RQ1 followed the evidence synthesis process methodology developed by the Health Information and Quality Authority (HIQA), particularly around the area of grey literature searching.[22]

The review questions were formulated in line with the PICOS (population, intervention, comparator, outcome and study design) or PICo (population, interest and context) frameworks, as appropriate. While all four questions were de novo searches conducted by the research team, RQ3 was partly informed by an existing published systematic review and meta-analysis.[8] Due to some concerns about the quality of this particular study based on the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) II checklist,[8] along with the need to expand the inclusion criteria and outcomes considered, it was decided by the research team to conduct

the searches from that study again.

2 Review question one: international models of specialist cardiac networks

2.1 Introduction

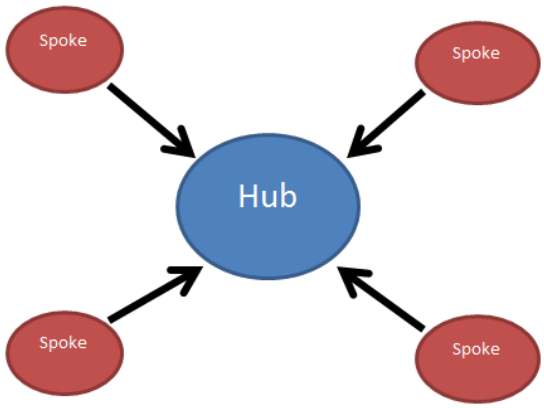
Specialist services for people with cardiac conditions such as acute coronary syndrome (ACS),[12] advanced heart failure,[23] cardiac arrhythmias[24] and adults with congenital heart disease (ACHD)[25] are generally provided in secondary or tertiary care facilities where access to appropriate levels of care are readily available. These secondary and tertiary care facilities are often organised into networks.[12] These networks extend beyond the traditional boundaries of individual hospitals, and may be considered a system defined as 'an integrated group of entities within a region coordinating the provision of diagnostic and treatment services.'[26] As noted in Section 1.3, a specialist cardiac network can be defined as a network of designated specialist cardiac centres with stratified capability, supported by an ambulance service, which aims to meet patients' needs and improve the quality, safety and efficiency of care.[6, 15]

There are a number of examples of specialist cardiac networks. These have typically been focused on the networked care of specific conditions, particularly the delivery of care in cardiac emergencies such as STEMI.[6] In the 1990s and 2000s, various trials found that primary PCI (that is, urgent balloon angioplasty to open the infarct-related artery during STEMI without the previous administration of thrombolysis), performed in a timely manner, provided significant mortality benefits over thrombolysis for patients with STEMI.[27] Additionally, patients that were transferred to PCI centres to receive primary PCI were found to have significantly improved outcomes compared with patients who received thrombolysis in non-PCI centres.[28-30] In 2003, the European Society of Cardiology (ESC) first recommended that STEMI care be regionalised with the aim of coordinating services, eliminating unnecessary delays and increasing the proportion of patients who receive primary PCI.[31] The current 2019 ESC guidelines on myocardial revascularisation recommend that 'the pre-hospital management of STEMI patients should be based on regional networks that are designed to deliver reperfusion therapy effectively in a timely fashion, and to offer primary PCI to as many patients as possibly.' This is a class I recommendation (meaning that there is evidence that the intervention is beneficial, useful or effective) and based on level B evidence (meaning that the data are derived from a single randomised controlled trial (RCT) or multiple large non RCTs).[12]

For STEMI patients in particular, who require early reperfusion and minimal time delays,[32] a typical system or network may comprise the emergency medical services (EMS) providers, referral hospitals that do not perform PCI and receiving hospitals that

perform high volumes of primary PCI.[26] One model of networked care that has been implemented across many healthcare conditions is the 'hub and spoke' model.[33] The 'hub and spoke' model of organisation design can be defined as an integrated delivery model which arranges service delivery into a network where the full array of complex procedures are centralised to a 'hub' centre and this is complemented by secondary establishments ('spokes') that offer a much more limited array of services (Figure 2.1).[33] The 'spoke' centres triage and transfer patients requiring a greater level of care to the 'hub' centres. 'Hub and spoke' models have been associated with greater efficiencies and quality of care, standardising processes across a network. However, they have also been criticised for potentially increasing congestion at 'hub' centres, downgrading 'spoke' hospitals and for increasing distances to services particularly for patients living in rural areas.[33]

Figure 2.1: Hub and spoke model



Use of a 'hub and spoke' model has also been recommended for other aspects of cardiac care. For example, a 2018 position statement by the Heart Failure Association of the ESC, recommends the establishment of 'hub and spoke' models for advanced heart failure management. The proposed model would see an advanced heart failure unit as the 'hub', working closely with specialised heart failure units in local hospitals and the 'spokes' in primary care or general cardiology units.[23]

Although specialist cardiac networks have been recommended for some time, especially in the area of STEMI care, it is unclear how these networks are organised in practice. Furthermore, contextual information from international networks, that may be relevant to the Irish healthcare system, may help to inform national health policy. The aim of this scoping review was therefore to identify and describe existing models of specialist cardiac networks, primarily focusing on countries most relevant to the Irish healthcare system.

2.2 Methods

2.2.1 Review question

What international models for specialist cardiac networks exist that might be applicable to the Irish healthcare system?

- What are the key characteristics and features, in terms of service design and delivery, of best practice models for the delivery of cardiac care, primarily focusing on countries with most relevance to the Irish healthcare system?
- What information is available from comparable jurisdictions on the design and operating plans for the networked provision of cardiology services?

Table 2.1: PICo for RQ1

Population	Adults (18 years or older) presenting with cardiac problems such as acute coronary syndrome (ACS), heart failure and heart arrhythmias, or with adult congenital heart disease (ACHD) in need of acute and chronic (including cardiac rehabilitation) specialist cardiac services. Also included are adults requiring access to cardiac diagnostics (both invasive and non-invasive), genetic testing and investigative services, as well as adults requiring access to cardiac syncope clinics, electrophysiology and catheterisation laboratories.
Interest	Provision of hospital-led cardiology care via a clinical network of services in high-income countries that are comparable to Ireland.
Context	Key characteristics and features of networks (for example, type of network, configuration, staffing, services offered, delivery of service). Key performance indicators.

2.2.2 Methods

Given the broad nature of the review question, it was decided to undertake a scoping review. A scoping review can be defined as a form of evidence synthesis that addresses an exploratory research question aimed at mapping key concepts, types of evidence, and gaps in research related to a defined field by systematically searching, selecting, and synthesising existing evidence.[34] Scoping reviews are generally preferable to systematic reviews when the purpose is to provide a comprehensive overview of a broad topic, rather than to determine the efficacy or effectiveness of a specific intervention.[16] Importantly, scoping reviews still provide

a high standard of rigour and transparency.[16, 19] The review adhered to the Arksey and O'Malley six-stage framework,[35] and the reporting followed the PRISMA extension for scoping reviews (PRISMA-ScR).[19] The six stages of the Arksey and O'Malley framework are as follows:

1. identifying the research question
2. identifying relevant studies
3. study selection
4. charting the data (that is, data extraction)
5. collating, summarising and reporting the results
6. consultation.[35]

The scoping review framework follows the main systematic reviewing principles; however, it allows for more flexibility in terms of inclusion and exclusion criteria, pays less attention to quality appraisal and is more focused on presenting a thematic overview of findings rather than determining any definitive effect estimate.

This scoping review was conducted in two phases: firstly providing a broad overview of specialist cardiac networks, and secondly providing a more in-depth analysis of selected cases studies.

The first phase of this scoping review involved a systematic search of the literature with the aim of identifying and characterising a broad range of specialist cardiac networks. Networks were considered relevant if they were based in countries with a very high human development index (HDI) score (top 30 of the 2018 scale)[36] or if they were from another EU country.[37] This phase was conducted in line with the six stages of the Arksey and O'Malley scoping review framework.[35]

The second phase involved conducting detailed case studies from specialist cardiac networks from three countries or regions that may be applicable to the Irish setting due to similarities in terms of patient population, healthcare system and economy. Due to the exploratory nature of this scoping review question, an iterative approach to case study selection was adopted which was informed by the first phase of the scoping review and feedback from the Steering Group. The three case studies selected were: the Emilia-Romagna region in Italy, Catalonia in Spain and strategic clinical networks in England. The former two were selected as they were well described in the literature[38-54] and based on their relative similarities to Ireland in terms of population, healthcare system and in particular the high gross domestic product (GDP) of these regions.[55] England was included due to the review team's knowledge of the existence of strategic clinical networks in England,[56] along with its relative similarities to Ireland in terms of demographics, GDP and organisation of healthcare.[55]

2.2.3 Search strategy

Electronic searches were conducted in PubMed, Embase, CINAHL Plus and the Cochrane Library (which includes the Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the National Health Service Economic Evaluation Database (NHS EED)) for the period 1 January 2008 to 13 March 2019. The search strategy used database-specific search terms (Appendix 1, Table A.1). Other search methods used included forward citation searching of eligible articles, hand searching relevant journals (*Heart*, *European Heart Journal*, *Journal of the American College of Cardiology*, *Canadian Journal of Cardiology*, *Catheterization and Cardiovascular Interventions*) and systematic reviews, and searching reference lists of included articles.

Grey literature sources were also searched (Appendix 2), with a particular emphasis on the websites (professional bodies, departments of health and HTA agencies) for the chosen comparator countries. Additionally, the first five pages of Google and Google Scholar were searched. Furthermore, Steering Group members were asked to identify relevant models from their national and international links. Due to significant advances in cardiology and in particular with regards to PCI practices and perioperative management, it was agreed with the Steering Group that only studies published since 2008 would be included.[8, 57] Studies published prior to 2008 were only included if they were referenced in included studies and considered pertinent.

2.2.4 Selection criteria

For the first stage of study selection, duplicates and clearly irrelevant records (for example pre-clinical studies) were removed by one reviewer. Two reviewers then independently reviewed the remaining titles and abstracts according to the inclusion and exclusion criteria (Table 2.2), with any disagreements being resolved through discussion, and a third reviewer where necessary. Subsequently, all potentially eligible records included in full-text screening were independently reviewed by two reviewers, with any disagreements being resolved through discussion, and a third reviewer where necessary. All records that were excluded after full-text screening are reported along with the reason for their exclusion in Appendix 6, Table A.22.

Any study, website, personal communication or policy document that described an existing adult cardiac clinical network (as defined below), located within a very high HDI country or EU country were included according to the inclusion and exclusion criteria set out in Table 2.2. Inclusion was limited to existing clinical networks for specialist cardiac services (even if based on a pilot study); descriptions of theoretical networks were excluded.

Table 2.2: Inclusion and exclusion criteria for RQ1

Inclusion Criteria	Exclusion Criteria
▪ The subject of the article is cardiac clinical networks ▪ The cardiac clinical network is hospital-led or is cardiologist-led if care is delivered across settings ▪ The cardiac clinical network is managed and hierarchical with a clear administrative structure specific to the network ▪ The cardiac clinical network manages acute myocardial infarction and or heart failure and or cardiac arrhythmias and or grown-up congenital heart disease and or cardiac rehabilitation and or provides access to cardiac diagnostic, genetic testing and investigative services, cardiac syncope clinics, electrophysiology or catheterisation laboratory ▪ The described clinical network is located in a high-income country that would have similarities to the Irish population and healthcare system (this includes the top 30 countries of the 2018 Human Development Index (HDI) or any EU country).	▪ Stroke networks ▪ Primary care-led networks ▪ Studies that focus on the provision of primary prevention services ▪ Non-managed networks ▪ Research networks ▪ Information networks ▪ Communities of practice ▪ Studies that utilised clinical networks to obtain samples for their study ▪ Focus is on changes to emergency medical services protocols (for example ambulance by-pass protocols) that are not related to cardiac clinical network formation ▪ Focus is on changes to in-hospital protocols (for example implementation of 'Code STEMI' protocol) that are not related to cardiac clinical network formation ▪ Publication before 2008 (except if referenced in an included publication and considered pertinent) ▪ Networks for paediatric cardiac conditions (<18 years old) ▪ Unreliable source ▪ Not current practice ▪ Inadequate information on the network (such as conference abstracts that have not been published in full) ▪ Reviews, editorials or commentaries.

As described in Section 1.2, the following definitions of clinical networks which were agreed with the National Review's Steering Group were used in this review:

- managed clinical networks — groups of clinicians who deliver services across the boundaries between healthcare professions and the different sectors of the

health system.

- network models of cardiac care with a hierarchical structure — networks made up of healthcare organisations, as well as the individuals within them, with an overarching administrative structure and with a focus on integration and coordination of clinical services; also known as integrated service delivery.

In order to minimise the risk that the included data did not accurately represent current practice due to the high level of grey literature, particular attention was given to the reliability of the source as well as the currency of the data, when screening studies. Stakeholders from identified networks were contacted if additional information was required.

2.2.5 Data extraction and management

The data were extracted from all included records that were considered to be current and potentially applicable to an Irish setting. Data extraction was performed by one reviewer, double checked by another reviewer and, where necessary, a third reviewer was consulted to resolve any disagreements. The data extraction tool was initially piloted by all three reviewers on two networks comprising ten records, [38-47] using Microsoft Excel. The extraction tool was then modified based on this piloting exercise to ensure consistency with the review question

The following data were extracted from each record:

- country
- cardiac condition(s)
- year of network establishment
- population served by network (that is, the catchment area)
- configuration of network
- distances between 'hub' and 'spoke' hospitals
- surgical back-up
- intervention components (if relevant)
- monitoring of performance / KPIs
- author-reported temporal changes in KPIs.

For data management purposes, the results of the search were exported to Covidence (www.covidence.org). Duplicates were identified and removed. Covidence was then used to manage citations and perform title and abstract screening. A flow diagram using PRISMA guidelines was generated to report the selection process and all results (Figure 2.2). Endnote X7.4 was used for reference management.

2.2.6 Quality appraisal/risk of bias assessment

The key objective of scoping reviews is to provide an overview of existing evidence regardless of methodological quality or risk of bias.[19] Quality appraisal or risk of bias assessment are therefore generally not recommended and hence were not conducted for this review question.

2.2.7 Data synthesis

Where different models of specialist cardiac networks were identified and described, a narrative synthesis of the results was conducted. The identified network was considered to be the unit of analysis for this review, rather than the record(s) that referred to the network.

Results are presented in two main tables; Appendix 3 provides an overview of all identified ACS-related networks (that is, ACS, STEMI or non ST-elevation myocardial infarction (NSTEMI) networks) (Table A.7) as well as networked care for other cardiac conditions (that is, heart failure, out of hospital cardiac arrest (OHCA), ACHD and cardiac arrhythmia) (Table A.8). These tables are summarised in the main text (Table 2.3 and Table 2.4).

The case studies were conducted by one reviewer, and double checked by another. These case studies were based primarily on information retrieved from the findings of the scoping review, and were supplemented by targeted searches of healthcare system,[58-61] demographic[62-64] and economic[55, 65-67] information pertaining to these regions.

2.2.8 Protocol deviations

Protocol deviations are listed in Appendix 10.

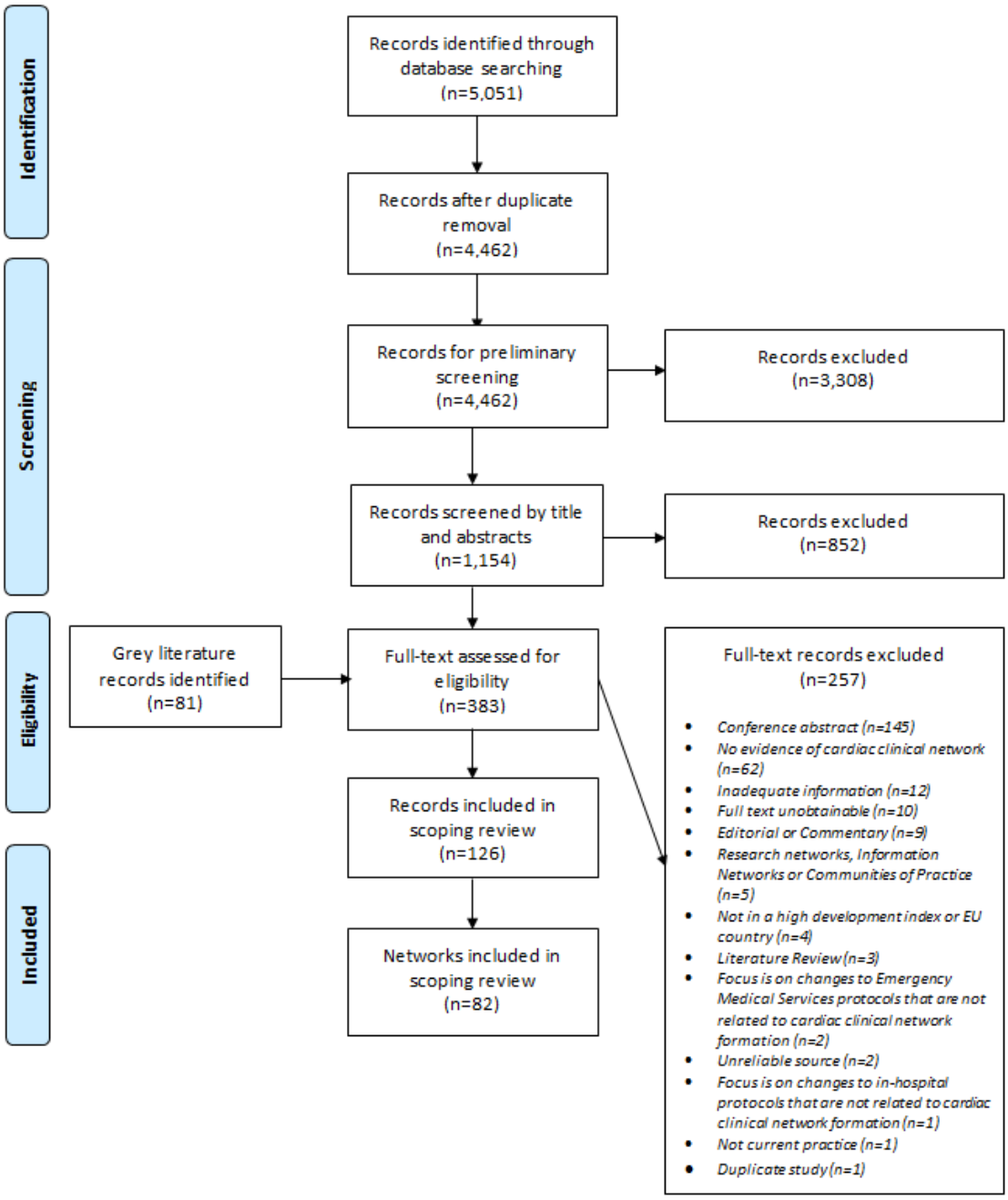
2.3 Results

2.3.1 Search results

The search of listed electronic databases identified 4,462 potentially relevant records after duplicates were removed. After the exclusion of clearly irrelevant records through a preliminary screening process, 1,154 records were screened independently by two reviewers, with a further 852 references excluded based on titles and abstracts. Eighty-one potential records were identified through searches of the grey literature and other sources and were added to the full-text review stage. A total of 383 full texts were assessed for eligibility. Of these, 257 references were excluded (Appendix 6, Table A.22) according to the inclusion and exclusion criteria (Table 2.2). This resulted in 126 records being included in the review, describing 82

unique networks (Figure 2.2).

Figure 2.2: PRISMA flow chart of included studies in RQ1



2.3.2 Characteristics of included networks

A summary of network characteristics is provided in Table 2.3 and Table 2.4, with more in-depth detail provided in Appendix 3 (Table A.7 and Table A.8).

Table 2.3: Table of characteristics of included acute coronary syndrome-related networks

Cardiac condition network type	Networks per countr	Year of establishment and configuration o network	PCI, 24/7 PCI and non-PCI centres per network	Population served pe network (millions)	Key performance indicators measurec across all networks
n=118 studies describing n=75 networks: STEMI networks (n=52), ACS networks, (n=22) NSTEMI network (n=1)	n=21 countries. Australia (n=11) Austria (n=2) Belgium (n=1) Canada (n=6) Croatia (n=1) Czech Republic (n=2) Denmark (n=1) France (n=2) Germany (n=5) Ireland (n=1) Italy (n=7) Japan (n=1) New Zealand (n=1) Poland (n=1) Portugal (n=1) Romania (n=2) Spain (n=2) Sweden (n=2) The Netherlands (n=2) UK (n=6) US (n=18)	**Year of network establishment:** Range = 1995-2018 Average= 2006 **Hub and spoke network:** Yes = 11 No = 0 Unclear = 64 **Surgical backup in network:** Yes = 17 No = 5 Unclear = 53	**PCI centres per network:** Range = 1-33 Median = 2 **24/7 PCI centres per network:** Range **=** 0-33 Median = 1 **Non-PCI centres per network:** Range **=** 0-98 Median = 9.5 **Ratio of non-PCI to PCI centres per network:** Range = 0-43 Median = 4 **Ratio of non-PCI to 24/7 PCI centres per network:** Range = 0-43 Median = 5 **Maximum distance between PCI centre and non-PCI centre within each network (km):** Range: 11-430 Average: 113.2	**Total population served per network:** Range = 0.182-19.0 Median = 1.0 **Population per PCI centre:** Range = 0.085-5.0 Median = 0.476 **Population per 24/7 PCI centre:** Range = 0.120-5.0 Median = 0.680	Time-to-treatment (n=65) Mortality/Survival (n=60) PCI complications (n=33) Reperfusion strategy (n=33) Medications (n=18) Healthcare utilisation (n=12) Neurological function (n=4)

Key: ACS – acute coronary syndrome; km – kilometres; NSTEMI – non ST elevation myocardial infarction; PCI – percutaneous coronary intervention; STEMI – ST elevation myocardial infarction.

Table 2.4: Table of characteristics of other (not ACS-related) included cardiac networks

Cardiac condition network type	Networks per country	Year of establishment and configuration of network	Population served per network (millions)	Key performance indicators measured across all networks
n=9 studies describing n=7 networks: HF networks (n=2) ACHD networks, (n=2) OHCA networks (n=2), and chronic IHD plus AF network (n=1)	n=7 countries. Austria (n=1) Canada (n=1) France (n=1) Spain (n=1) Sweden (n=1) UK (n=1) US (n=1)	**Year of network establishment:** Range = 2002-2018 Average= 2011 **Hub and spoke network:** Yes = 1 No = 0 NA/Unclear = 6 **Number of hub centres:** Range = 1-4 Average = 2 **Number of spoke centres:** Range = 2-27 Average = 13 **Ratio of spoke to hub hospitals:** Range = 1-19 Average = 8.9 **Surgical backup in network:** Yes = 2 No = 0 NA/Unclear = 5	**Total population served per network (n=2)*:** Range = 0.421-6.60 Median = 3.510	Mortality/Survival (n=4) Time-to-treatment (n=2) Medications (n=2) Procedural complications (n=1) Reperfusion strategy (n=1) Neurological function (n=1)

*The population served by each network was only reported in two networks.
Key: ACHD – adult congenital heart disease; AF – atrial fibrillation; HF – heart failure; IHD – ischaemic heart disease; km – kilometres; NA – not applicable; OHCA – out of hospital cardiac arrest; PCI – percutaneous coronary intervention.

2.3.3 Cardiac network types

From all 126 included records,[38-43, 45-54, 68-177] 82 unique specialist cardiac networks were identified. Of these, 75 were ACS-related cardiac networks. Specifically, the scoping review identified 52 STEMI networks, 22 ACS networks (with protocols for STEMI patients as well as for NSTEMI and or unstable angina patients), and one NSTEMI network (Table 2.3). There was evidence of overlap between cardiac networks. For example, in total, six OHCA networks were identified, four of which were designed as combined ACS and OHCA networks (Table 2.4). Similarly, three cardiac arrhythmia networks were identified, two of which overlapped with pre-existing ACS networks, and one combined network for patients with chronic ischaemic heart disease or cardiac arrhythmias. Seven of the 82 identified networks were not directly related to or linked with ACS networks; specifically, two heart failure networks, two ACHD networks, two OHCA networks were identified along with the combined network for both chronic ischaemic heart disease and cardiac arrhythmias (Table 2.4).

2.3.4 Country of networks

Of the 82 identified networks, 19 were located in the US; 11 in Australia; seven each in Italy, the UK and Canada; five in Germany; three each in France, Austria, Sweden and Spain; two each in the Czech Republic, the Netherlands and Romania; and one each in Belgium, Croatia, Denmark, Japan, New Zealand, Poland, Ireland and Portugal (Table 2.3 and Table 2.4).

2.3.5 Year of network establishment

While the review was limited to records published in 2008 or later, some networks had been in existence for decades; one Australian network was established in 1995.[146] However, most ACS-related networks were established in the mid-2000s, with the average year of establishment being 2006, soon after the publication of the 2003 ESC recommendations for regionalisation of STEMI care (Table 2.3).[31] Conversely, the relatively few non-ACS networks identified appeared to be more recent in their development. The oldest identified non-ACS network was established in France in 2002,[73] and the most recent established in 2018 (Table 2.4).[129]

2.3.6 Configuration of networks

Twelve networks explicitly stated that they were configured as 'hub and spoke' networks. Six of the seven identified Italian networks explicitly described themselves as 'hub and spoke' networks. The only identified Italian network that did not explicitly describe itself as such was the Ristemi network serving Rivoli in northwest Italy.[166] Only one of the 19 identified US networks explicitly stated that it was a

'hub and spoke' network, and that was the Carolinas healthcare system network.[172] The remaining networks (n=70) did not clearly state how they were configured; however, the way the majority of these networks were organised was synonymous with 'hub and spoke' models (Table 2.3 and Table 2.4). Only one non-ACS network classified itself as a 'hub and spoke' model.[69]

Because of advances in PCI technology and techniques as well as advances in adjunctive pharmacotherapy and increased operator experience, the need for emergency cardiac surgery for unsuccessful PCI has significantly declined.[178-180] Clinical outcomes and complications rates have previously been found to be similar between PCI sites with and without on-site surgical back-up.[181] International guidelines pertaining to on-site surgical back-up are discussed in greater detail in Chapter 3 (RQ2). With regard to on-site surgical back-up, 19 ACS networks explicitly stated that they had this facility in at least one centre within their network. Five networks stated that they did not have this facility within their network and hence required access to surgical services in neighbouring networks if required. The remaining networks (n=58) did not clearly state whether or not they had this facility within their network (Table 2.3 and Table 2.4).

Across all 75 ACS-related networks, the number of PCI-capable centres per network ranged from one to 33, with a median of two. Thirty-five of the 75 ACS-related networks had a single PCI-capable centre. Los Angeles STEMI network, which serves a population of approximately 10 million people, had 33 PCI-capable centres.[82, 100, 148, 158] The number of non-PCI-capable centres in the included networks ranged from 0 (in an urban network in Vienna)[45, 108, 113, 116, 120, 121] to 98 (in a state-wide network in North Carolina),[45, 100, 102, 103, 113, 117, 118, 138] with a median of 9.5. The ratio of non-PCI to PCI capable centres ranged from 0 to 43, with a median of four (Table 2.3 and Table 2.4).

Not all PCI centres in the identified networks offered a 24/7 service. At least one identified network did not provide a 24/7 PCI service. This network was located in Mackay in Queensland, Australia, which serves a region of very low population (182,000 inhabitants).[146] Although at least 55 of the 75 ACS-related networks provided a 24/7 PCI service in at least one hospital within the network, it was not clear whether a 24/7 service was provided in 19 other networks. The Vienna STEMI network described a system whereby, on a rotating basis, one of the five part-time PCI centres opened 24/7 alongside one other PCI centre that provided a continuous 24/7 service. That is, at any one time, at least two 24/7 PCI centres were available in the city.[45, 108, 113, 116, 120, 121] Part-time PCI centres that provided limited hours of PCI service (usually as part of a network that also had 24/7 PCI centres) were described in eight networks. Specifically, these part-time PCI centres were located in networks in Auckland, Vienna, Eastern Austria, Mackay, Catalonia, Sweden, Dallas

and Ireland. With regard to the non-ACS related networks, at least three provided 24/7 services, however the service hours of the other networks was not clearly described (Table 2.3 and Table 2.4).

2.3.7 Distances between hospitals in networks

The maximum distance between a PCI centre and a non-PCI centre within a network ranged from 11km to 430km, with an average maximum distance of 113.2km. The shortest distance was in Ottawa, which is an urban STEMI network,[45, 126] while the longest distance was in New Zealand, between the PCI-capable hospital in Auckland and the non-PCI capable hospital in Hastings, Hawkes Bay. However, this particular hospital in Hastings was not normally part of the Auckland network and only accepted patients on very rare occasions – the furthest hospital that was permanently within this network was located 313km away from Auckland in Kaitaia, which was 3 hours and 43 minutes away via land transport.[128] The furthest non-PCI hospital permanently affiliated with a PCI centre was identified in Minnesota, where one hospital was located 338km away from the PCI centre. In this network, half-dose thrombolysis was provided to STEMI patients, who were being transferred from 'zone 2 hospitals' to the PCI centre in Minneapolis for early PCI intervention. These zone 2 hospitals were located between 100 and 338km away from the PCI centre.[45, 100, 111, 113, 130, 136, 157] Given the evidence on the relative benefits of primary PCI over thrombolysis in STEMI patients,[100] a number of other ACS networks such as Vienna, France, the Mayo Clinic, North Carolina and Ireland, outline specific protocols for pre-hospital or in-hospital administration of thrombolysis if the anticipated time from first medical contact to balloon inflation generally exceeded 90 to 120 minutes.[113, 176]

Information regarding distance was not provided by non-ACS related networks.

2.3.8 Population served by networks

The population served by each ACS network ranged from 182,000 in Mackay, Australia[146] to 19 million across the country of Romania,[160] with a median of 1 million. The population served per PCI centre ranged from 85,000 inhabitants per PCI centre in rural South Australia[162] to 5 million inhabitants per PCI centre in Charlotte, North Carolina,[172] with a median of 476,000 inhabitants per PCI centre. Focusing specifically on the population served per 24/7 PCI centre, this value ranged from 120,000 inhabitants per 24/7 PCI centre in Essen, Germany[84, 87, 106, 107, 115] to 5 million inhabitants per 24/7 PCI centre in Charlotte, North Carolina,[172] with a median value of 680,000 inhabitants per 24/7 PCI centre. However due to the presence of competition in the US healthcare system,[100] it is possible that the 5 million inhabitants reportedly served by the network in North Carolina[172] had a choice of an alternative network (for example, the state-wide North Carolina

network) [45, 100, 102, 103, 113, 117, 118, 138] hence the actual population served by this network may be substantially lower. Excluding this US network, the Eastern Denmark STEMI network has the largest population served per PCI centre and per 24/7 PCI centre (2.5 million inhabitants per centre).[91, 121, 152] By comparison, the Irish ACS programme serving a total population of approximately 4.6 million inhabitants,[182] has a catchment population of approximately 511,000 inhabitants per PCI centre and approximately 920,000 inhabitants per 24/7 PCI centre.[174-177]

Focusing solely on European networks did not result in any substantially different findings. The population served per PCI centre ranged from 120,000 to 2.5 million inhabitants, with a median of 500,000 inhabitants per PCI centre. The population served per 24/7 PCI centre ranged from 120,000 to 2.5 million inhabitants, with a median of just over 600,000 inhabitants per 24/7 PCI centre.

Networks located in Germany, the US and Italy were consistently found to have the lowest population served per PCI centre and 24/7 PCI centre. Conversely, networks located in Denmark, Romania and Canada were consistently found to have the largest populations served per PCI centre and 24/7 PCI centre (Table 2.3). Although some Australian PCI centres served small populations,[146] others served very large populations,[68] possibly reflecting the vast geographic and demographic differences across the country.

Information on the population served was not provided by non-ACS related networks.

2.3.9 Monitoring of outcomes

Key performance indicators are essential tools in monitoring the performance of healthcare services, providing reliable information about current and desired standards, and are critical as a tool for improving the quality of care delivered to a population.[183] A multitude of KPIs were evaluated across the networks. These were: mortality or survival (n=64); time-to-treatment (for example, door-to-balloon time and door-to-needle time) (n=67); procedural complications (for example, bleeding) (n=34); reperfusion strategy (that is, whether thrombolysis or primary PCI was used) (n=34); medications (for example, on discharge) (n=20); healthcare utilisation (for example, length of hospital stay) (n=12); and neurological function (that is, whether or not patients returned to normal cerebral functioning after a cardiac arrest) (n=5).

2.3.10 Author reported findings

The impact of the ACS networks as reported by the study authors is outlined in Table A.7. Caution is required when interpreting these findings as they were not

subject to quality appraisal. Furthermore, the nature of reporting varied as some studies conducted a pre-post study comparing before and after network establishment, whereas other studies only had data available since establishment of the network. Therefore, many of these data are not comparable. In general, study authors reported increased efficiencies as a result of the establishment of the networks in terms of improvements in time-to-treatment (24 of 32 networks) and the proportion of patients receiving primary PCI (15 of 15 networks). Although overall improvements were predominantly reported, there was more uncertainty regarding the impact of network establishment on mortality (12 of 21 networks), complication rates (two of six networks) or healthcare utilisation (one of three networks). Two networks reported an increase in complication rates in their network based on annual audit data.[76, 110, 140, 184]

With regards to non-ACS related networks, very little evidence was available to support their efficiency or effectiveness (Table A.8).

2.3.11 Components of the networks

Broadly speaking, the majority, if not all, of the ACS-related networks were based on the same underlying principles:

- centralisation of 24/7 PCI services to a very limited number of geographically central, high-volume hospitals
- centralised dispatching of ambulances, mobile intensive care units or helicopters, depending on the geographic region
- ECG (electrocardiogram) performed by paramedics or on-board physicians/nurses (often with electronic transmission of the ECG to the PCI centre)
- primary PCI as the preferred reperfusion strategy for STEMI
- pre-hospital or in-hospital thrombolysis according to a defined protocol if the PCI procedure could not be delivered within a defined time (typically linked to an international guideline recommendation)
- activation of the PCI centre to inform staff of incoming STEMI patient
- bypassing of non-PCI capable centres and emergency departments
- patient delivery straight to the catheterisation lab (cath lab).

Additionally, some networks specifically mentioned how patients were repatriated back to their local non-PCI hospital that had a coronary care unit (CCU), soon after the PCI was performed, provided that there were no complications.[38-54, 71, 74-76, 81, 87, 96, 109, 110, 112, 114, 121, 127, 132, 140, 164, 168, 169, 171]

The non-ACS networks were more heterogeneous in their design and delivery. Of the two heart failure networks described, one located in Austria was primarily based

on telemedicine and specifically mobile health (mHealth) monitoring of physiological signs and symptoms with close linkage between primary care doctors and nurses and in-hospital physicians.[87, 134, 135, 170] The other heart failure network, located in France, did not have any telemedicine component, but was more focused on the multidisciplinary management of the patient and in particular the enhanced medical care between a network of primary care doctors and cardiologists.[73] No heart failure network was identified that was organised as a 'hub and spoke' model.

Six OHCA networks were identified. These were located in the Czech Republic,[153] Pennsylvania,[69] Ontario,[83] Los Angeles,[82] London[143] and Minneapolis.[136] Four of these networks were organised alongside pre-existing ACS-related networks,[82, 136, 143, 153] another was organised alongside a severe sepsis network[69] and one was a standalone OHCA network.[83] Similar to ACS-related networks, the OHCA networks were organised around access to 24/7 PCI centres, since many incidences of OHCA are caused by STEMI. Additionally, the Ontario network implemented a 'post cardiac arrest consult team' providing a multidisciplinary approach to OHCA management,[83] and the Pennsylvania network implemented telemedicine consultations between the 'hub' and 'spoke' hospitals to better utilise scarce cardiology resources.[69]

Three cardiac arrhythmia networks were identified. These were located in Apulia, Italy[76, 85, 86] the Netherlands[168] and Barcelona, Spain.[101] Two of these were organised alongside pre-existing ACS-related networks,[76, 85, 86, 168] and the other was established alongside a chronic ischaemic heart disease (IHD) network. In Apulia, a regional prehospital ECG network with a single telecardiology 'hub' for the emergency medical service was implemented in 2004. Although the main aim of the network was to quickly diagnose STEMIs using ECGs and trigger the relevant protocols, cardiac arrhythmias were also diagnosed and triaged within this network.[76, 85, 86] In a pre-existing ACS-related network in Midden, in the Netherlands, a protocol to prevent sudden cardiac death was implemented which involved intensive treatment of ACS patients and close monitoring after the index event.[168] In Barcelona, an integrated model of care between primary care and cardiologists was established with the aim of improving care for patients with chronic IHD or atrial fibrillation. This particular model of care involved enhanced cooperation between the cardiologist and GPs with a greater number of primary care and telemedicine consultations with the patient.[101]

Two adult congenital heart disease (ACHD) networks were identified located in Sweden[141] and the UK.[129] Limited information was provided regarding how the Swedish network operated. In the UK ACHD network, a system is described whereby four hospitals provided 'level one' specialist surgical ACHD services, two hospitals provided 'level two' specialist ACHD cardiology services and another two hospitals provided 'level three' ACHD outpatient services.[129]

Two of the networks identified were located on the island of Ireland. The ACS Programme[175-177] was established by the HSE in Ireland in 2013 and is a national programme that serves a population of 4.6 million. It comprises 28 non-PCI centres and nine PCI-capable centres. Six of the centres are designated primary PCI centres, five of which are open 24 hours a day, 7 days a week. On average, each of the nine PCI-capable centres serves a population of approximately 511,000 people (on average, each 24/7 PCI centre serve a population of almost 1 million). Since the establishment of the ACS Programme there have been reported improvements in primary PCI reperfusion rates, time-to-treatment and mortality. The other Irish network is a primary PCI service established in Northern Ireland in 2011.[112] The network involves two 24/7 PCI centres and serves the population within a 60 minute drive from each centre. The centre in west of the country is also contracted to provide primary PCI services for the Donegal region in Ireland. The Northern Ireland network carried out 451 primary PCI procedures in 2015/2016 with 99.9% of eligible patients treated with primary PCI. They reported comparable call-to-balloon times, door-to-balloon times and 30-day mortality rates to networks in England and Wales.

2.3.12 Case study one: Emilia-Romagna Acute Coronary Syndrome Network

Emilia-Romagna is a region in northern Italy with a population of approximately 4.45 million inhabitants (Figure 2.3).[62] Approximately 24% of the population are 65 years or older.[62] Emilia-Romagna covers an area of 22,446 km², 90% of which is rural.[65] The estimated GDP of this region was €157 billion in 2017, making it one of the most developed regions in Europe.[55]

The Italian healthcare system operates at a regional level, and is predominantly publicly funded through a national corporate tax. Private healthcare plays a very limited role in the Italian healthcare system, with only 5.5% of the population availing of voluntary health insurance. Primary and inpatient care are provided free at the point of use.[59] The regional authorities coordinate and control local health units, each of which is a separate unit within the National Health Service (Servizio Sanitario Nazionale). These local health units are responsible for assessing healthcare needs, planning service delivery and providing comprehensive care to the local population.[150]

Following the publication of guidelines by the ESC in 2003, which endorsed regionalisation of STEMI care,[31] a policy decision was made by the regional authority of Emilia-Romagna to develop and implement a territorial cardiac network, using a 'hub and spoke' model.[46] After gradual expansion there are currently 48 hospitals in this cardiac network, consisting of 10 invasive 'hub' (that is, PCI-capable) hospitals with CCUs and cath labs available on a 24/7 basis, 14 non-invasive (that is,

non-PCI capable) 'spoke' hospitals with CCUs, and 24 non-invasive 'spoke' hospitals with internal medicine departments and cardiology consultant services, but without CCUs.[38]

Figure 2.3: Map of the Emilia-Romagna Region in Italy

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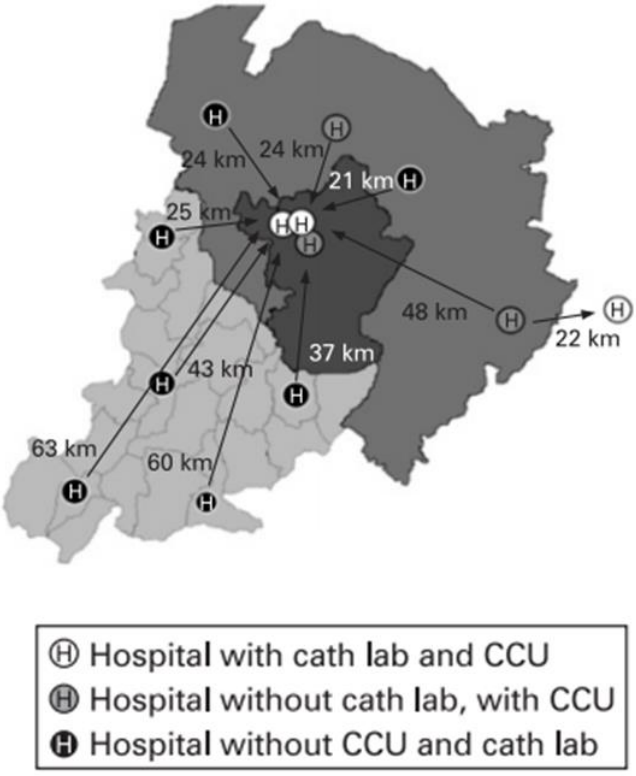
Bologna is a province within Emilia-Romagna and has a population of 1.01 million inhabitants.[62] Bologna has its own 'hub and spoke' network which sits within the wider network of Emilia-Romagna. In Bologna, there are currently 12 hospitals within this network consisting of two PCI 'hub' hospitals with a high-volume cath lab available on a 24/7 basis, and 10 'spoke' hospitals without PCI facilities (Figure 2.4).[41] An additional hospital with PCI capability, in a neighbouring province, acts as a 'hub' hospital for one of the peripheral 'spoke' hospitals, as indicated in the map (Figure 2.4). The Bologna network has an estimated catchment population of 500,000 inhabitants per 24/7 PCI centre with a maximum distance between 'hub' and 'spoke' hospitals of approximately 63km (Figure 2.4).

Figure 2.4: The hub and spoke network of Bologna province.



CCU – coronary care unit. Reproduced by permission of the British Medical Journal

Primary PCI in the 'hub' hospitals is the preferred reperfusion strategy for patients presenting with STEMI, within the Emilia-Romagna network.[39, 46] Patients that present with STEMI at a 'spoke' hospital are rapidly and systematically transferred to a 'hub' hospital for primary PCI, according to their risk profile, taking into account any potential time delays.[39] The emergency calls from the region are received by the 118 EMS, which coordinates the ambulance service.[38] Telemedicine with ECG transmission from the ambulance has been gradually implemented throughout the network, and enables the EMS to transmit ECGs to the nearest 'hub' hospital for diagnosis of STEMI, and signals cath lab activation and emergency department (ED) bypass protocols if necessary.[41] Repatriation back to the CCU of the 'spoke' hospital closest to patient's home is recommended within 24 hours of performing the primary PCI procedure provided that there is no serious complications.[41] The Emilia-Romagna network has an estimated catchment population of 410,000 inhabitants per 24/7 PCI centre with a maximum distance between 'hub' and 'spoke' hospitals of approximately 63km.

Patients with NSTEMI or unstable angina self-presenting or triaged by the 118 EMS, are usually admitted to the closest hospital ('hub' or 'spoke'). Only patients with haemodynamic or electrical instability are referred directly to a 'hub' centre. All other NSTEMI or unstable angina patients are risk assessed in the 'spoke' hospital, and a

coronary angiography procedure (if indicated) is scheduled in the nearest 'hub' hospital,[38] ideally within 72 hours of 'spoke' hospital admission as per guideline recommendations.[185] Patients transferred for invasive procedures are transferred back to the referring hospital on the same day, following a two- to six-hour observation in the cath lab recovery room.[38]

2.3.13 Case study two: Catalonia Codi Infart STEMI network

Catalonia is an autonomous region in the northeast of Spain with a population of approximately 7.5 million inhabitants (Figure 2.5).[64] Approximately 19% of the population are 65 years or older.[186] Catalonia covers an area of 32,108 km^2,[186] of which 79.5% is rural.[66] The estimated GDP of this region in 2017 was €223 billion, and hence is one of the most developed regions in Europe.[55]

Catalonia has complete autonomy in the area of healthcare.[61] There is universal coverage in the region and hence healthcare is provided free at point of use. Although the whole population of Catalonia is covered by publicly financed health services, about 20% of the population use private healthcare coverage or use both public and private systems.[61]

Figure 2.5: Map of Catalonia Region in Spain

In 2007 a policy decision was made by the Health Department of Catalonia, based on advice from the Catalan Society of Cardiology, to implement an organised network of STEMI care across the entire autonomous region of Catalonia.[54]

The Codi Infart STEMI network was implemented in 2009. The Codi Infart network has four key components:

- ambulances staffed by physicians or nurses trained in ECG interpretation and thrombolytic administration

- an EMS dispatch centre to coordinate logistics between the various hospitals and ambulances
- ten primary PCI centres, five of which provide 24/7 services
- a registry to prospectively monitor KPIs, such as mortality, procedural complications and time-to-treatment, across the entire network.[53, 54]

The Codi Infart network is activated once a patient is diagnosed with a STEMI based on ECG and clinical guidelines. Primary PCI is the preferred reperfusion strategy, and STEMI patients are transferred to their nearest primary PCI centre. Once clinically stable, patients are transported to a CCU in a non-PCI referral hospital closer to the patient's home in order to reduce pressures on the primary PCI centres.[48] Patients treated with thrombolysis are transferred to a primary PCI centre immediately if thrombolysis fails.[53] The Codi Infart network has an estimated catchment population of 1.5 million inhabitants per 24/7 PCI centre with an unknown maximum distance between 'hub' and 'spoke' hospitals.

An analysis of the cost-effectiveness of this network was published in 2015. A before and after study design was used. Costs included the cost of hospitalisation, procedures and additional personnel; no additional infrastructure was required to establish the network, so these costs were not included. Outcomes considered were 30-day mortality and quality-adjusted life years (QALYs).[52] The study found a substitution effect after the establishment of the network, with the use of primary PCI increasing (from 31% to 89%) and thrombolysis decreasing (from 37% to 3%). Use of rescue PCI and no reperfusion also decreased (from 11 to 4% and 21 to 4%, respectively). Due to technological improvements in PCI delivery, the average length of hospital stay decreased as did the mean cost per patient. Thirty-day mortality was reported to decrease from 7.5% to 5.6%. Overall the Catalan STEMI network was reported by the author to be a cost-efficient use of resources.

2.3.14 Case study three: Strategic Clinical Networks in England

The population of England is approximately 55.62 million inhabitants[63] and covers an area of 132,937 km^2.[187] Approximately 18% of the population are 65 years or older.[63] The estimated GDP of England was €2,007 billion in 2017.[67]

Healthcare in England is publicly funded through general taxation, and is provided free at the point of use.[60] Approximately 10% of the UK population have private health insurance as a means to avail of faster access to care.[60]

The English healthcare system underwent significant reform in 2013. Two hundred and eleven clinical commissioning groups (CCGs) were established, which are clinically led statutory National Health Service (NHS) bodies, and are responsible for the planning and commissioning of healthcare services for their local regions. NHS

England, an independent body which remains at 'arm's length' from the Department of Health, is responsible for commissioning other services, allocating funds to the CCGs as well as holding the CCGs to account. NHS England commissions mostly primary care services such as GPs and pharmacists, whereas the CCGs commission mostly secondary care services such as urgent and emergent care, but also commission community health services.(58)

During the period of reform, strategic clinical networks (SCNs) were introduced across England. These SCNs were established 'in areas of major healthcare challenge where a whole system, integrated approach is needed to achieve a real change in quality and outcomes of care for patients.' The overarching aims of these networks were to reduce variation in services and to encourage innovation. The first SCNs were established in 12 regions across England in 2013, initially focusing on the areas of cancer; cardiovascular disease; maternity and children; and mental health, dementia and neurological conditions.

Strategic clinical networks are non-statutory bodies, meaning that they do not have a legal duty to commission health services, and this responsibility remains with the CCGs and NHS England. Rather, the role of the SCN is to develop care pathways within geographical regions, enhancing integration across primary, secondary and tertiary care, and ultimately improving care for patients. The clinical and network directors of the SCNs are accountable to NHS England through local area teams.(56) Led by a clinical director and network manager, SCNs consult with key stakeholders including patients, members of the public, CCGs, local area teams and providers on a strategic plan which are agreed to by the local area team's director.(188)

Although clinical networks existed in England prior to 2013, there was variation in how they operated and were governed.(56) Approximately 28 cardiac networks existed across England in 2011.(189) In line with the introduction of SCNs in 2013, these networks are currently organised into approximately 25 local area teams, which sit within the 12 SCNs.(190) For example, the London SCN encompasses a cardiac network with the following focus areas:

- ACS
- cardiac arrhythmias
- cardiac surgery
- heart failure
- cardiology
- cardiovascular disease prevention.

Auditing of services is a key component of ACS networks across all of England (and the rest of the UK). The British Cardiovascular Intervention Society (BCIS) registry, which has been in existence since 1994, collects data from all PCI procedures

performed in UK hospitals with the aim of evaluating the quality of care, driving quality improvement and providing data for research.[191] Reporting of data is mandatory and the registry has quality systems in place to ensure the data are accurate and reliable. The variables reported include patient demographics, indications for PCI, operator details, technical aspects of the procedure and adverse outcomes including complications and mortality up until discharge. Reports are produced annually and provide findings at the national, network and hospital level.[192]

2.4 Discussion

This scoping review identified and characterised 82 specialist cardiac networks across 21 countries with a range of structures and populations served. Seventy-five of these 82 networks were ACS-related, and in particular STEMI networks, so these networks dominated our findings. In general, the identified ACS-related networks were organised around a limited number of geographically central 'hubs' that provided high-volume primary PCI services, and usually (but not always) these services were provided 24/7. EMS were streamlined to reduce time delays while transferring patients and were often optimised to conduct, interpret and transmit ECGs. In rural networks in particular, EMS often had defined protocols to administer thrombolysis before or during transfer to primary PCI centres. ACS-related networks generally had bypass and cath lab activation protocols delivering the patient straight to the cath lab and hence avoiding any potential delays in the ED. Some networks also had clear repatriation protocols in place to reduce pressures on primary PCI centres. The majority of networks monitored KPIs to evaluate the performance of the network over time. ACS-related networks generally reported improvements in efficiencies, with some networks reporting improvements in clinical outcomes. Clear governance structures also appear to be important for sustainability and development of specialist cardiac networks, as evidenced by the strategic clinical networks in England.

Although the ACS-related networks had many commonalities, there were clear differences in how they were organised in different countries. In agreement with previous international surveys,[193, 194] we found that ACS-related networks located in Germany, the US and Italy had the smallest catchment areas. Conversely, networks located in Denmark, Romania and Canada, were found to have the largest catchment areas. Reasons for this disparity are complex and are likely due to a combination of healthcare system, healthcare professional, political, economic, epidemiologic, demographic and geographic factors.[100, 193, 194] For example, in 2014, Germany recorded the highest rate of PCI and primary PCI procedures across all of Europe and other member states of the ESC (that is, the non-European former Soviet Republics such as Ukraine, Eastern Mediterranean countries such as Israel

and Northern African countries such as Egypt).[195] This relatively large demand for PCI in Germany may have resulted in a large number of centres being required. Conversely, one of Europe's largest STEMI networks is located in Denmark, serving a catchment area of 2.5 million inhabitants. This particular network was created as a result of a merger between two PCI centres in 2011 following a political decision and in the context of significant hospital centralisation and reform across Denmark.[91, 121, 152, 196] Of note, despite doubling capacity in the Danish PCI "mega centre" to approximately 1,000 annual primary PCI procedures, the quality and efficiency of care remained high. The authors of this particular study attributed the successful merger to good governance, significant training and resources, and a highly organised pre-hospital triage system.[152]

In 2010 the results of a survey on the care of STEMI patients in European countries were published. Based on results from 30 national and or regional registries, the authors suggested that the 'optimal' population served per 24/7 PCI centre was in the range of approximately 300,000–1.1 million inhabitants.[194] The authors estimated that a catchment population within this range would result in the region of 200–800 primary PCI procedures per year per centre, which the authors argued would be sufficient to sustain a high volume of PCI procedures[194] (which has been associated with improved outcomes in patients).[8] The authors added that a PCI centre serving fewer than 300,000 inhabitants may not perform a sufficient volume of procedures for staff to maintain technical competency and conversely a population significantly more than 1 million inhabitants may result in congestion in the 'hubs'.[194] Of the 46 included ACS-related networks, where a population per 24/7 PCI centre could be calculated, 33 ACS-related networks (72%) were determined to sit within this 'optimal' range of 300,000–1.1 million inhabitants (Table A.7). Similarly, 70% of included European ACS networks were found to sit within this threshold. The Irish ACS Programme has a catchment population of approximately 920,000 inhabitants per 24/7 PCI centre and was found to be generally on par with international ACS networks from an organisational standpoint. Importantly, some PCI networks sit outside this range and report good outcomes, for example, the Eastern Danish PCI centre (as discussed above) which serves a population of 2.5 million inhabitants.[152]

Although ACS-related networks are well described in the literature, very little was found (seven of the 82 networks identified) regarding specialist cardiac networks dealing with cardiac arrhythmias, heart failure or ACHD. No literature was found regarding networks for cardiac syncope, cardiac rehabilitation or access to diagnostic and genetic testing services. Often the few non-ACS networks identified were organised alongside existing ACS-related networks, leveraging the 'hub and spoke' model to their advantage, moving more specialist services into high-volume 'hubs' and less specialist procedures to 'spoke' centres.[76, 85, 86, 168] However, the literature

was quite sparse in this area and may reflect the relatively recent emphasis on networked care for these other specialist cardiac services.[197]

Regarding heart failure models in particular, despite the plethora of evidence to support the effective and safe delivery of services across transitions of care through multidisciplinary strategies,[198-200] nurse-led models,[201, 202] pharmacist-led models[203, 204] or telemonitoring interventions,[205-208] very few networked models of care for heart failure were identified that were hospital-led or had cardiologist oversight.[73, 134, 135, 170] Moreover, what also emerged was the ambiguity surrounding some of the terminology used to describe heart failure networks. For instance, literature referring to the German Heart Failure Network was retrieved in our searches, but on inspection these networks were a registry of heart failure patients who were admitted to hospitals, rather than any managed or hierarchical system of hospitals working together to provide integrated heart failure care.[209, 210]

Huitema et al. describe a novel model of integrated heart failure care – the 'spoke-hub-and-node' model for Canada.[197] The authors proposed a multi-level system with shared protocols, consisting of a 'spoke' (for stable, low-risk patients cared for in primary care settings), a community 'hub' (for stable, moderate-risk patients cared for in local hospital settings) and a tertiary 'node' (for high-risk patients with complex needs possibly requiring heart transplant, cared for in advanced/specialist cardiac centres). A key component of this proposed model is two-way communication between the various levels of care, using face-to-face visits along with phone and telemedicine consultations.[197] Various national and international guidelines and position statements have also recently recommended that 'hub and spoke' type networks for heart failure management should be established at a regional level.[23, 211] Therefore, it is expected that within the next few years, these heart failure networks, which consist of greater integration between primary, secondary and tertiary care, should become more commonplace.

The main strength of this scoping review was the broad and comprehensive search undertaken by a team of reviewers with experience in conducting evidence syntheses. Close involvement of the Steering Group for the National Review during development of the protocol for this project, allowed for a more focused search of countries with the most relevance to an Irish healthcare system. This scoping review of specialist cardiac networks has provided a broad overview of how such networks are organised. Furthermore, the three case studies have provided more in-depth information regarding how such networks function in reality. The combination of this 'breadth and depth' analysis provides a detailed picture of the current state of specialist cardiac networks.

One of the key limitations of the study was the scoping nature of the review.

Although the scoping review methodology was essential to answering our broad question in relation to identifying and characterising specialist cardiac networks, it cannot address effectiveness or safety questions. Furthermore, in line with scoping review methodology, quality appraisal was not conducted.[35] Though author-reported outcomes were extracted in this study, these findings must be viewed with caution as a scoping review methodology is not designed to provide a definitive answer. Rather, these findings are presented here to illustrate that, in general, the establishment of these networks would appear to be associated with improvement in efficiencies and perhaps improvements in effectiveness, and highlight that some uncertainties remain in this area. Hence a further systematic review of effectiveness and safety, involving quality appraisal, may be required to determine whether specialist cardiac networks are effective and safe.

Due to the contextual and organisational variations between networks, it is likely that any planned systematic review would not be able to combine findings, and a narrative synthesis subject to substantial caveats may be all that is feasible. Furthermore, since international guidelines have strongly recommended that cardiac care be regionalised [12, 212] and healthcare systems are likely to move in this direction regardless, the potential to undertake research examining effectiveness of different network structures and the usefulness of a systematic review may be questionable.

The review team were limited by the data that were reported in the studies. Information on staffing was inconsistently reported and often referred to staffing in different components of the network; hence these data were not extracted. In describing the design of an ACS network, the number of PCI-capable sites and the distance between networked hospitals was typically reported and these data were extracted. The context for these data is important. The distance the patient has to travel to access care is obviously important in the context of elective procedures. However, in the case of STEMI, the outcome of interest is the time-to-treatment, therefore the overall length of time it takes from first medical contact or diagnosis to treatment initiation, rather than the distance travelled per se. Time-to-treatment outcomes (for example, door-to-balloon time) are commonly reported as performance measurements (KPI) for audit and quality improvement purposes.

It is inevitable that other specialist cardiac networks exist in the examined jurisdictions which were not included in this review. However, if the network had not been described or evaluated in the literature or in any of the grey literature sources that we examined, we were unlikely to identify this network. An important area for future research may be to create a registry of national and international specialist cardiac networks, where key personnel from each network could be surveyed or even self-report the characteristics and KPIs of their network. Important lessons can

be learned from such an approach[121] and this may prove a vital resource for policymakers.

2.5 Conclusion

This scoping review identified and characterised 82 specialist cardiac networks from across 21 countries. ACS related networks constituted the majority of identified networks. Certain commonalities were found across these networks; however important organisational differences were also identified. Limited information was identified regarding networks for other cardiac conditions; however these networks are likely to develop and advance over the coming years due to recent guideline recommendations.

2.6 Key points

- A scoping review was undertaken to identify and describe models of specialist cardiac networks currently in existence, primarily focusing on countries most relevant to the Irish healthcare system.
- A specialist cardiac network can be defined as a network of designated, specialist cardiac centres with stratified capability, supported by an ambulance service, which aims to meet patients' needs and improve the quality, safety and efficiency of care.
- Eighty-two specialist cardiac networks were identified located across 21 countries, of which 19 were located in the US.
- Of the 82 identified networks, 75 were related to ACS, and seven were non-ACS related. In total, six OHCA networks were identified, four of which overlapped with ACS networks. Three cardiac arrhythmia networks were identified, two of which overlapped with pre-existing ACS networks and one was a combined network for patients with chronic ischaemic heart disease or cardiac arrhythmias. 'Hub and spoke' models featured prominently in ACS related networks.
- Not all PCI centres in the identified networks offered a 24/7 service. At least 55 of the 75 ACS-related networks provided a 24/7 PCI service in at least one hospital within the network. Part-time centres had established protocols for the timely transfer and management of patients requiring primary PCI for STEMI.
- The maximum distance between a PCI centre and a non-PCI centre within an ACS network ranged from 11 to 430km, with an average maximum distance of 113.2km.
- The population served per 24/7 PCI centre ranged from 120,000 to 2.5 million inhabitants with the majority of identified networks (72%) sitting within the 'optimal' range of 300,000 to 1.1 million inhabitants.
- Key performance indictors commonly monitored across networks were mortality/survival, neurological function, procedural complications, time-to-treatment, healthcare utilisation, choice of reperfusion strategy and discharge medications.

3 Review question two: organisational and service specification recommendations for centres providing percutaneous coronary interventions (PCI)

3.1 Introduction

As outlined in Section 1.2, the network model of cardiac care can be defined as a hierarchical structure focused on integration and coordination of clinical services. A typical format includes a 'hub and spoke' model whereby the 'hub' is typically a comprehensive, specialist cardiac centre capable of providing a full array of highly specialised treatments. 'Hubs' are complemented by secondary establishments, the 'spokes', which provide a more limited array of services, with onward referral of patients for care that falls outside the scope of that provided by the 'spoke'.[33] Management of STEMI has been identified as one of the most time-critical components of a specialist cardiac service. The goal for these patients is to achieve rapid reperfusion of the infarct-related artery. Primary PCI (PCI without prior administration of fibrinolytic agents) is the preferred method of treatment when it can be rapidly performed within defined timelines, but there are patient, hospital, and geographic factors that can affect delivery times.[212] When it is not possible to perform primary PCI within the defined timeline, thrombolysis is generally considered the optimal reperfusion strategy. It was noted that the staffing, equipment and organisation of specialist interventional cardiology services capable of delivering PCIs and particularly primary PCI will likely also fulfil the service requirements for other complex and acute cardiac conditions. Therefore, a decision was made in consultation with the National Review's Steering Group to use PCI as the exemplar procedure to develop the evidence to inform the design of the 'hub' of a 'hub and spoke' model.

This question was answered by conducting a de novo systematic review of international guidelines and standards examining recommendations for the configuration of centres providing PCI, including primary PCI. The quality of guidelines was formally assessed and similarities and differences between the guidelines explored, including the evidence underpinning the criteria. Data extracted includes recommendations for minimum volume standards for primary PCI, in order to help inform future service configuration.

Although guidelines were the main source of this information, other guidance documents such as position papers, practice documents and recommendations were also included.

3.2 Methods

3.2.1 Review question

What organisational and service criteria do national or international guidelines, recommendations, position papers and standards specify for centres providing percutaneous coronary interventions (PCI) for cardiac conditions in adults?

The population, area of interest and context for this question are summarised in Table 3.1. For the purpose of this systematic review, the umbrella term 'guidance documents' was used to describe the guidelines, position papers, recommendations and standards identified for inclusion in this review.

Table 3.1: PICo for RQ2

Population	Adults (18 years or older) requiring PCI (primary or elective) for cardiac conditions
Interest	Criteria for PCI centres (primary or elective) including: ▪ Institutional facilities ▪ Institutional volume ▪ Operator volumes ▪ Surgical cover ▪ Staffing levels ▪ Time/distance to treatment ▪ Monitoring of standards and or KPIs
Context	Guidance documents: ▪ Guidelines (international, national or regional) ▪ Position papers ▪ Recommendations ▪ Standards

3.2.2 Search strategy

Electronic searches were conducted in PubMed, Embase, CINAHL Plus and the Cochrane Library (which includes the Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the National Health Service Economic Evaluation Database (NHS EED)) for the period 1 January 2008 to 17 January 2019. The search strategy used database-specific search terms (Appendix 1, Table A.2). Grey literature sources were also searched (Appendix 2), along with the first five pages of Google and Google Scholar. In addition, Steering Group members were asked to identify relevant clinical guidelines from their national and international links. Other search methods

used included scanning the reference list of included studies and the reference lists of studies (such as editorials and guideline reviews) captured by the initial search, which were highlighted as potentially referencing eligible guidance documents during title and abstract screening.

Due to substantive changes in the management of myocardial infarction, and evolving casemix, searches were limited to guidelines published since 2008.[57] Although language was not an exclusion criterion, relevant non-English language guidelines for which a reasonable English translation could not be obtained were excluded.

3.2.3 Selection criteria

For the first stage of study selection, duplicates and clearly irrelevant records were removed by one reviewer. Two reviewers then independently reviewed the remaining titles and abstracts according to the inclusion and exclusion criteria (Table 3.2), with any disagreements being resolved through discussion, and a third reviewer where necessary. Subsequently, all potentially eligible records included in full-text screening were independently reviewed by two reviewers, with any disagreements being resolved through discussion, and a third reviewer where necessary. All records that were excluded after full-text screening are reported along with the reason for their exclusion in Appendix 6, Table A.23.

Guidance documents that provided criteria for centres providing PCI (primary PCI or PCI for any indication) in adults (18 years or older) were collated and the data extracted. Guidance documents that only reported time-to-treatment criteria, or related to specific sub-populations (for example, left main PCI (LMPCI), chronic total occlusion (CTO), congenital heart disease) or specific PCI techniques (for example thrombectomy, trans-radial access) were collated and are reported in Appendix 5, but were not subject to data extraction or quality assessment.

Table 3.2: Inclusion and exclusion criteria for RQ2

Inclusion Criteria	Exclusion Criteria
Guidance document that: ▪ provides criteria for centres performing PCI in adults (18 years or older) for cardiac conditions ▪ is evidence-based (meets at least one of the following criteria – based on a literature review – based on expert consensus	Guidance document that: ▪ does not specify criteria for PCI ▪ published before 2008 ▪ does not include criteria for adult (18 years and older) services ▪ has been superseded by a more recent version ▪ is specific to a single hospital/

methods, which are described in the document – affiliated with a recognised society.) ▪ are novel or adapted from other guidelines, recommendations or standards.	catheterisation lab or local area ▪ that adopt other guidelines, standards and recommendations in full ▪ that do not provide numerical values for criteria ▪ excluded from review but identified and collated – if recommendation was only in relation to time-to-treat criteria – specific sub-populations (e.g. LMPCI, CTO, Congenital Heart Disease) or – specific techniques (e.g. thrombectomy, trans-radial)

Key: CTO – chronic total occlusion; LMPCI – left main percutaneous coronary intervention; PCI – percutaneous coronary intervention.

3.2.4 Data extraction and management

Data extraction was performed independently by a minimum of two people with any disagreements being resolved by discussion, and where necessary, a third reviewer. The data extraction tool was piloted initially. For data management purposes, the results of the search were exported to Covidence (www.covidence.org). Duplicates were identified and removed. Covidence was then used to manage citations and perform title and abstract screening. A flow diagram using PRISMA guidelines was generated to report the selection process and all results (Figure 3.1). Endnote was used for reference management.

The following data were extracted for each included guidance document:

- Country or region
- Year of dissemination
- Search dates
- Development team
- Funding organisation
- Methods to evaluate evidence
- Methods for formulating criteria
- Criteria for centres performing PCI specifically relating to:
  - Institutional facilities
  - Institutional volume
  - Operator volumes

- Surgical cover
- Staffing levels
- Time/distance to treatment
- Monitoring of standards/KPIs.

Guidance document criteria for PCI centres in general were extracted, as well as for those centres performing primary PCI for STEMI.

3.2.5 Quality appraisal

Two reviewers independently assessed the methodological quality of included guidance documents, using a standardised critical appraisal instrument, with any disagreements resolved through discussion. The Appraisal of Guidelines for Research and Evaluation Two (AGREE II) tool was used,[213-215] with the tool initially piloted by two reviewers.

AGREE II scores were calculated and reported in accordance with the AGREE II manual, including the average percentage score.[213] Inter-rater agreements were also assessed by subtracting the scores of the two reviewers; differences of more than two for any item were discussed to reach consensus, with a third reviewer to arbitrate if necessary.

3.2.6 Assessment of currency and content

According to the ADAPTE methodology,[20] when possible, the included guidance documents were assessed for currency by evaluating the dates covered by the literature search (listed in Appendix 3, Table A.9).

Where reported, criteria for centres providing primary PCI were summarised in addition to general criteria for PCI centres. The evidence base underpinning each criterion (for example, based on systematic review, expert opinion, and so forth) are described in Appendix 3 (Table A.9). The guidelines were arranged by geographic region, then alphabetically by country, then in chronological order.

3.2.7 Protocol deviations

Protocol deviations are listed in Appendix 10 — Protocol deviations 10.

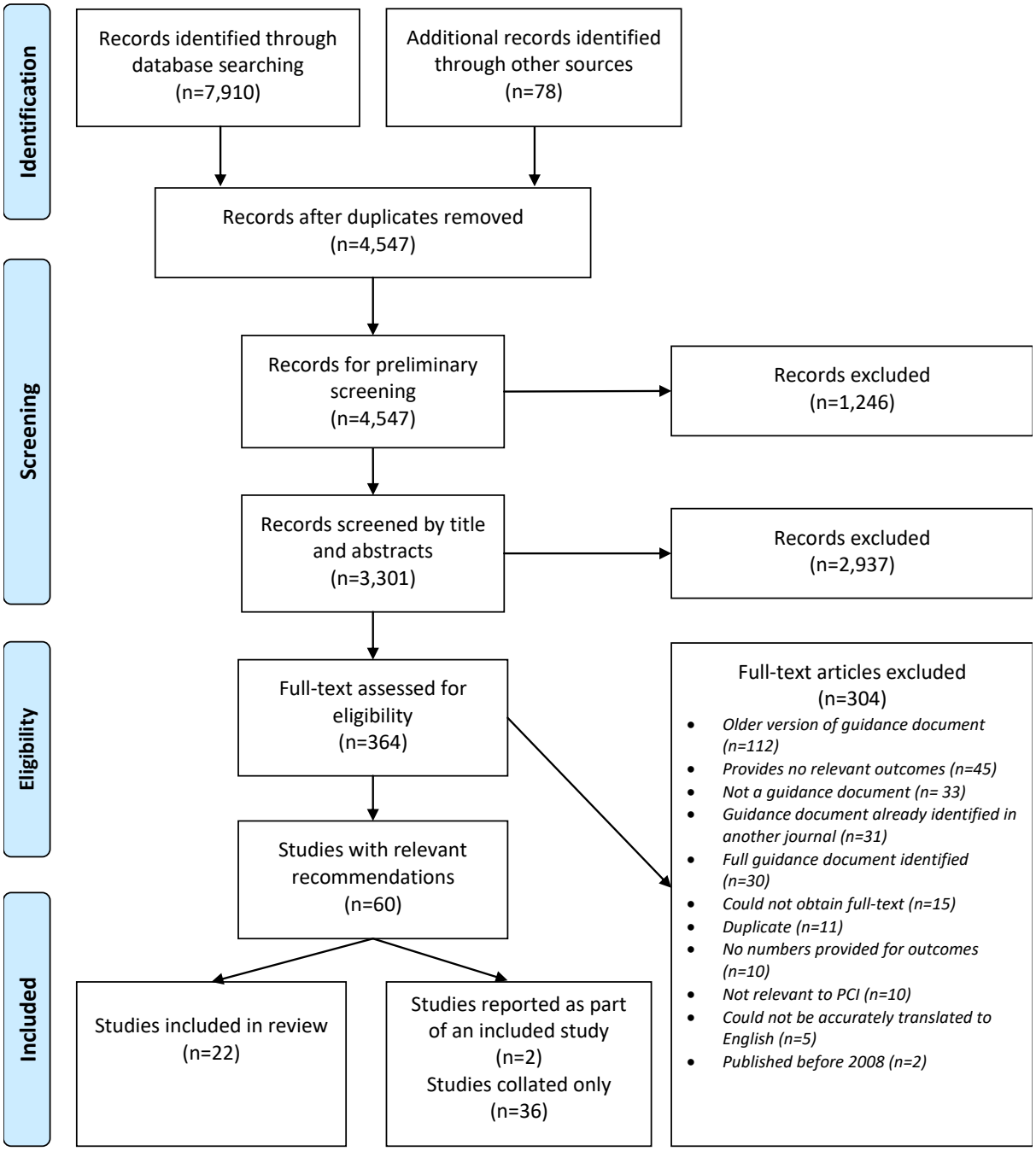
3.3 Results

3.3.1 Search results

The search of listed electronic databases identified 7,910 potentially relevant records; 78 potential records were identified through searches of the grey literature and other sources. After the removal of clearly irrelevant records and duplicates,

3,301 records were screened independently by two reviewers. Of these, 2,937 were excluded on the basis of title and abstract screening, leaving 364 documents assessed for full text eligibility. In total, 60 guidance documents were included as being relevant as per the inclusion criteria (Figure 3.1). Of these, 22 were included in the full review. The remaining 38 included two progress reports,[176, 177] which were analysed in conjunction with an included earlier guidance document,[175] and 36 which provided information on specific topics only and were collated as additional information (time-to-treatment (n=30),[212, 216-244] specific techniques (n=3),[245-247] specific sub-populations (n=1),[248] chest pain units (n=1)[249]) and development of new PCI services (n=1)[250] and are presented in Appendix 5. The excluded full-text articles, along with the reasons for their exclusion, are listed in Appendix 6, Table A.23.

Figure 3.1 PRISMA flow chart of included guidance documents for RQ2



3.3.2 Characteristics of included guidance documents

Table 3.3 provides a summary of the key characteristics of the included guidance documents. Further details of each of these documents can be found in Table A.9 in Appendix 3.

Table 3.3 Table of characteristics of included guidance documents

Organisation (year)	Country/ region	Title	Recommendations relating to: IF	IV	OV	SL	SC	TD	MS
Asia-Pacific									
CSANZ (2014a)[251]	Australia & New Zealand	Position Statement for Competency in Percutaneous Coronary Intervention (PCI)		✓	✓				✓
CSANZ (2014b)[252]	Australia & New Zealand	Position Statement for Performance of and Support Facilities for a Primary Percutaneous Coronary Intervention (PCI) Service	✓	✓	✓	✓	✓	✓	✓
CSANZ (2016)[253]	Australia and New Zealand	Guidelines on Support Facilities for Coronary Angiography and Percutaneous Coronary Intervention (PCI) including Guidelines on the Performance	✓	✓	✓	✓	✓	✓	✓
API (2011)[254]	India	Guidelines for Management of Acute Myocardial Infarction		✓	✓			✓	
JCS (2013)[255]*	Japan	Guidelines for Elective Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease		✓		✓	✓		
Europe									
ESC/EACTS (2019)[12]	Europe	2018 ESC/EACTS Guidelines on myocardial revascularization	✓	✓	✓			✓	✓
DGK (2015)[256]†	Germany	Guidelines to establish and operate catheterization laboratories and hybrid operating rooms/hybrid laboratories (3rd edition 2015)	✓			✓			
HSE/RCPI (2012)[175]**	Ireland	Acute Coronary Syndromes Programme: Model of Care	✓			✓		✓	✓
SICI-GISE (2015)[257]†	Italy	Position Document SICI-GISE standards and guidelines for diagnostic laboratories and interventional cardiovascular	✓	✓	✓	✓	✓	✓	✓
NVVC (2016)[258]†	Netherlands	Practice Document for interventional cardiology	✓	✓	✓	✓	✓	✓	✓
PTK (2013)[259]†	Poland	Guidelines of the Association of Cardiovascular Interventions of the Polish Cardiac Society for certification of coronary diagnosis and percutaneous coronary intervention operators and invasive cardiology centers in Poland	✓	✓	✓				✓
SSC (2014)[260]	Switzerland	Institutional and operator recommendations for percutaneous coronary interventions	✓	✓	✓	✓	✓	✓	✓
NHS England (2013)[261]	England	2013/14 NHS Standard Contract for Cardiology: Primary Percutaneous Coronary Intervention (PPCI) (Adult)	✓	✓	✓			✓	✓
BCIS and BCS	UK	Percutaneous coronary intervention in the UK: recommendations for good	✓	✓	✓	✓	✓	✓	✓

Organisation (year)	Country/ region	Title	Recommendations relating to: IF	IV	OV	SL	SC	TD	MS
(2015)[262]		practice 2015							
BCIS (2016)[263]	UK	Primary Percutaneous Coronary Intervention for ST Elevation Myocardial Infarction Position statement for Facilities and Emergency Medical Staffing	✓	✓	✓	✓	✓	✓	✓
North America									
CCN (2013)[264]	Canada	Recommendations for the best-practice STEMI management in Ontario	✓					✓	✓
CCS (2015)[265]	Canada	The Canadian Cardiovascular Society Quality Indicators E-Catalogue - Quality Indicators for Percutaneous Coronary Intervention		✓				✓	✓
ACCF/SCAI (2012)[266]	USA	2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions Expert Consensus Document on Cardiac Catheterization Laboratory Standards Update	✓	✓	✓	✓		✓	✓
ACCF/AHA/SCAI (2013)[11]	USA	ACCF/AHA/SCAI 2013 Update of the Clinical Competence Statement on Coronary Artery Interventional Procedures	✓	✓	✓		✓		✓
SCAI/ACC/AHA (2014)[178]	USA	2014 Update on Percutaneous Coronary Intervention Without On-Site Surgical Backup	✓	✓	✓		✓	✓	✓
ACC/AHA/SCAI/AMA (2014)[267]	USA	ACC/AHA/SCAI/AMA – Convened PCPI/NCQA 2013 Performance Measures for Adults Undergoing Percutaneous Coronary Intervention		✓	✓				✓
SCAI (2016)[268]	USA	SCAI Expert Consensus Statement: 2016 Best Practices in the Cardiac Catheterization Laboratory		✓	✓	✓	✓		✓

Key: IF – institutional facilities; IV – institutional volume; OV – operator volume; SL – staffing levels; SC – surgical cover; TD – time/distance to treatment; MS – monitoring of standards.

ACC(F) – American College of Cardiology (Foundation); AHA – American Heart Association; AMA – American Medical Association; API – Association of Physicians of India; BCIS – British Cardiovascular Intervention society; BCS – British Cardiovascular Society; CCN –Cardiac Care Network of Ontario; CCS – Canadian Cardiovascular Society; CSANZ – Cardiac Society of Australia and New Zealand; DGK – German Cardiac Society; EACTS – European Association for Cardio-Thoracic Surgery; ESC – European Society of Cardiology; GISE – Italian Group of Hemodynamic Studies; JCS – Japanese circulation Society; NVVC – Netherlands Association of Cardiology; PTK – Polish Cardiac Society; RCPI – Royal College of Physicians in Ireland; SCAI – the Society for Cardiovascular Angiography and Interventions; SICI – Italian Society of Invasive Cardiology; SSC – Swiss Society of Cardiology.

* English revised digest version. Original Japanese versions published in 2011 and 2012.
† Guidelines translated into English using Google Translate
** Progress reports were published in 2015 (Heart Attack Ireland 2014)[176] and 2018 (Heart Attack Ireland 2016)[177] which were reviewed in combination with the 2012 document.

3.3.2.1 Country of origin

Of the 22 guidance documents included, three were from Australia and New Zealand,[251-253] two from Canada[264, 265], and five from the United States.[11, 178, 266-268] Ten were from Europe,[12, 175, 256-263] including three from the UK.[261-263] Three guidance documents from Ireland were included as a single study as the content was related.[175-177] One guidance document was included from India,[254] and one from Japan.[255]

3.3.2.2 Type of Guidance document

The majority of the 22 guidance documents identified themselves as either a 'guideline' (n=6)[12, 253-256, 259], a 'consensus statement/document' (n=5)[178, 264-266, 268] or a 'position paper/statement' (n=5).[251, 252, 257, 260, 263] Other types of guidance document included a 'clinical competence statement' from the American College of Cardiology (Foundation), American Heart Association and the Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI);[11] a 'practice document' from the Netherlands Association of Cardiology;[258] a 'service specification' document from NHS England;[261] a 'programme model of care' document from the Health Service Executive and Royal College of Physicians in Ireland (HSE/RCPI) in Ireland;[175-177] a report on performance measures from the ACC/AHA/SCAI/AMA (American Medical Association)[267] and a document on recommendations for good practice from the BCIS in the UK which was described as a guideline and a consensus statement.[262]

3.3.2.3 Composition of guidance document development team

Most guidance documents gave some information on the authors or development team. This was often limited to the list of members (between two[254] and 23[267] for those who listed the number of members) or a statement about who chaired the committee. Less than half of these guidance documents provided details on the role and expertise of the development team members.[11, 12, 175, 254, 255, 259, 263, 264, 266, 267]

3.3.2.4 Methods used to evaluate evidence and formulate recommendations

On the whole, the methods used to evaluate evidence and formulate recommendations were generally not well reported. For most of the guidance documents it was unclear how the evidence was collected and evaluated (n=12);[175, 251, 252, 255-257, 259, 261-263, 265, 266] some mentioned or referenced guidelines, but it was unclear if the evidence was taken directly from these guidelines.[175, 253, 254, 258, 262, 268] A review of the literature was undertaken for four of the guidelines,[11, 12, 178, 264] with two also using consensus of expert opinion.[11, 178] Consensus of opinion was stated as the method used to evaluate evidence in five guidance documents.[178, 264, 266-268] (255) To formulate recommendations, none of the guidance documents reported using

Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology; half (n=11) of the guidance documents reported no methods,[175, 178, 251-254, 256, 257, 260, 262, 263] while the other half reported expert consensus as the method.[11, 178, 255, 258, 259, 261, 264-268] Two guidance documents provided classes of recommendation based on predefined scales.[12, 255]

3.3.2.5 Outcomes reported

As outlined in Table 3.3, 16 guidance documents reported on institutional facilities for PCI centres.[11, 12, 175, 178, 252, 253, 256-264, 266] Nineteen made recommendations around institutional volume,[11, 12, 178, 251-255, 257-263, 265-268] while 17 made recommendations around operator volume.[11, 12, 178, 251-254, 257-263, 266-268] Surgical cover recommendations were made in 11 guidance documents,[11, 178, 252, 253, 255, 257, 258, 260, 262, 263, 268] and staffing level recommendations were made in 12 documents.[175, 252, 253, 255-258, 260, 262, 263, 266, 268] Recommendations on the monitoring of standards were made in 19 guidance documents.[11, 12, 175, 178, 251-253, 257-268] Recommendations with regard to time or distance to treatment were made in 15 of the 22 guidance documents.[12, 175, 178, 252-254, 257, 258, 260-266] Thirty additional guidance documents made reference to time or distance to treatment, but provided no additional information around specifications for a PCI centre.[212, 216-244] Therefore, as stated in section 3.2.3 these guidance documents were not quality-assessed, rather they were collated and listed in Table A.20 (Appendix 5) for information.

3.3.3 Primary Outcomes

An overview of recommendations can be found in Table 3.4. More detailed information on these recommendations can be found in Appendix 4. Some recommendations applied to more than one outcome category; where this happened, the recommendation was recorded in all appropriate categories.

3.3.3.1 Recommendations for PCI centre Institutional facilities

3.3.3.1.1 All PCI facilities

Sixteen of the guidance documents, mostly from Europe, reported on this outcome (Table 3.3). There was agreement between a number of the guidelines that a PCI centre must have:

- physiological assessment facilities (such as ECG, blood pressure, heart rate and oxygen saturation measurement equipment)[11, 253, 256, 257, 259, 260, 262]
- high-resolution digital imaging capacity with real-time transfer and archiving of images[11, 178, 252, 257, 259, 262]
- additional imaging or procedural tools (such as flow and pressure wires,

intravascular ultrasound (IVUS) and optical coherence tomography (OCT))[11, 178, 257-259, 262]

- cardiac laboratory equipment including intra-aortic balloon counter-pulsation pump (IABP), an anaesthetic machine and facilities to monitor anticoagulation[11, 252, 253, 256-259, 261-263]
- radiation protection, monitoring, and recording equipment[257, 258, 262]
- full resuscitation facilities including a defibrillator[11, 252, 253, 256-259, 261-263]
- disposable angioplasty equipment (including antithrombotic medications, guide catheters, guide wires, balloons and stents)[178, 257, 258, 262]
- a ventilator[256, 257, 259, 263]
- access to intensive care unit (ICU) or intermediate care unit.[253, 260] One guideline specified access to circulatory support and intensive care treatment for high-risk PCI procedures[12]
- systems in place to allow credentialing, governance, data gathering and quality assessment.[11, 266]

In addition, guidelines specified that equipment must be available and in good operating order,[11, 256] the centre must have full support and commitment from hospital administration[253] and it should have an on-call team available to deal with complications for at least 24 hours after the last procedure is performed.[253] The BCIS 2015 recommended that preferably two catheterisations laboratories should be available (in case of equipment failure). They also stated that if a second catheterisation laboratory was not available, then a non-cardiac radiology facility used for general radiology backup or a high-resolution portable fluoroscopy unit with a small image intensifier should be considered the minimum requirement.[262]

3.3.3.1.2 Additional requirements for primary PCI centres

In addition to the requirements laid out above, a number of guidelines agree that primary PCI centres should have:

- two cardiac catheterisation laboratories[175, 258, 261, 263, 264]
- availability 24 hours a day, 7 days a week[12, 175, 178, 257-261, 263, 264, 266]
- an extensive support system of specifically trained laboratory personnel,[11, 257] including interventional cardiologists, anaesthesiologists, intensive care physicians, nurses, radiographers and technicians[175, 257, 261] and cardiothoracic surgical and respiratory services[11]
- a network of services organised in collaboration with emergency/ambulance services[12, 175, 252, 257, 264]

- a CCU/ICU with adequate step down beds[175, 257, 259-261]
- a dedicated call service and ECG reception[175, 263]
- systems in place to allow patients to bypass the ED and be transferred directly to the catheterisation laboratory.[12, 263, 264]

In addition, in 2013 NHS England recommended centres should have contingency plans to deal with the rare occasions when the service may have to be withdrawn (such as adverse weather or major power failure);[261] HSE/RCPI 2012 guidelines recommend facilities to allow access to cardiac rehabilitation and secondary prevention prior to discharge;[175] and the Cardiac Care Network of Ontario (CCN) in Canada recommend inter-hospital arrangements for the repatriation of patients to the non-PCI hospitals after treatment.[264]

3.3.3.2 Recommendations for PCI centre - institutional volume

There has been extensive debate around what should be considered as the minimum number of cases an institution should perform per year in order to maintain optimal performance.[13] PCI techniques and post-procedure management have rapidly evolved over time and the casemix has changed as operators are undertaking PCI in patients at higher risk of complications due to more complex pathologies or comorbidities. It has been suggested that the influence of procedure volume on outcomes has diminished.[269] This issue is systematically evaluated in Chapter 4. Minimum volume recommendations varied from region to region and these differences are outlined in Tables A.14 and A.15.

3.3.3.2.1 Total PCI volume

The recommended minimum number of total PCI per year per PCI centre ranges from 200 procedures per year[11, 12, 178, 252, 260, 268] to 800 procedures per year for a supervisory centre.[258] The minimum of 200 procedures per year is stated in six of the guidance documents.[11, 12, 178, 252, 260, 268] In addition, the Cardiac Society of Australia and New Zealand (CSANZ) 2014 position statement also stated that at least 200 interventions per year were needed, but an ideal minimum per centre would be 400 interventions per year.[251] The Japanese Circulation Society 2013 guidelines recommend that institutes must perform a minimum of 200 cases of PCI and a minimum of 30 cases of 'open heart surgery, coronary or aortic bypass surgery' annually.[255] The ACCF/AHA/SCAI statement from 2013 suggests that those performing fewer than 200 cases per year must have systems in place to allow the close monitoring of clinical outcomes and additional strategies to ensure operators and other staff gain relevant experience through collaborative relationships with larger volume facilities.[11] The 2019 European Society of Cardiology (ESC) / European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines recommend that PCI

for stable coronary artery disease (SCAD) can be performed in institutions with a minimum of 200 PCI procedures per year, but that PCI for ACS should be performed in institutions performing more than 400 PCIs per year.

Three guidance documents recommended a minimum of 400 procedures per year.[257, 262, 265] One of these guidance documents stated that it is considered acceptable for institutions to perform fewer than 400 procedures per year when located in remote areas.[257] In addition, the ESC/EACTS 2019 guideline and ACCF/SCAI 2012 expert consensus document both recommend that institutions performing fewer than 400 procedures per year should collaborate with more experienced institutions.[12, 266]

Of the guidance documents identified for inclusion, the minimum institution volume recommended by the Netherlands Association of Cardiology (NVVC) practice document was the highest, recommending a minimum of 600 procedures per year.[258] They clarify within the guidance document that new centres should perform a minimum of 400 procedures per year for the first two years of operation, with a minimum of 600 procedures per year by the third year. They recommend supervisory centres should perform a minimum of 800 procedures per year.

The Association of Cardiovascular Interventions of the Polish Cardiac Society position paper had three levels of cardiac centre. For start-up invasive cardiology laboratories more than 240 PCI procedures per year is recommended; for advanced invasive cardiology laboratories more than 500 PCI procedures per year is necessary; while reference invasive cardiology laboratories are required to do more than 700 PCI procedures per year.[259]

In general, US guidance documents recommend more than 200 PCI procedures per centre per year, while European guidelines are more variable, ranging from 200 for the Swiss Society of Cardiology 2014[260] and ESC/EACTS 2019 guidelines[12] to 400 in the UK[261] and Italy[257] and 600 in the Netherlands.[258]

Institutional volume recommendations from the same organisation are not always consistent over time. In the US, the SCAI previously withdrew recommendations for a minimum threshold for institutional volume in 2014. This recommendation was later reinstated in a consensus statement in 2016.

In addition the BCIS statement on the development of new PCI services (Appendix 5, Table A.21) recommends a minimum of 200 therapeutic coronary interventions in the first year for new PCI services, with an increase to 400 cases per annum within three years.[250]

3.3.3.2.2 Primary PCI volume

The recommended minimum institutional volume for primary PCI ranges between 36 primary PCI procedures per year[11, 178, 251-254, 268] and 150 primary PCI procedures per year.[263] Guidelines from the US,[11, 178, 268] Australasia[251-253] and India[254] recommend a minimum of 36 primary PCI procedures per year, while two guidance documents from the UK (BCIS 2015 and NHS England 2013)[261, 262] both recommend a minimum of 100 primary PCI procedures per year. A more recent position statement from the BCIS recommends 150 primary PCI procedures per year unless there is extreme geographical isolation to justify a lower volume service.[263] Both BCIS guidance documents recommend annual review and the consideration of a network approach which rationalises the number of PCI centres if fewer than 150 primary PCI procedures per year are performed[263] or fewer than 300 primary PCI procedures per year are performed.[262] The Swiss Society of Cardiology guidance document recommends a minimum of 300 elective PCI procedures per year as sufficient for a institute to perform primary PCI.[260]

Of note, is the BCIS statement on the development of new PCI services (Appendix 5, Table A.21). Based on UK epidemiologic data, this statement estimates, that for new 24/7 primary PCI centres, a hospital would need to serve a population of at least 200,000 inhabitants to achieve a minimum of 100 primary PCI procedures per annum. If a single hospital were to provide primary PCI services during normal daytime working hours only (that is, 9am to 5pm Monday to Friday), the BCIS statement estimates that a hospital would need to serve a population of at least 500,000 inhabitants to achieve a minimum of 100 primary PCI procedures per annum.[250]

3.3.3.3 Recommendations for PCI operator volume

Minimum operator volumes varied from region to region and these differences are outlined in Appendix 4, Tables A.14 and A.15.

3.3.3.3.1 Total PCI volume

The recommended minimum operator volume for PCI is between 50[260] and 150[258] PCI procedures per year. One Swiss and three US guidance documents recommend either a minimum of 50 PCI procedures per year[260] or 100 procedures over two years.[11, 178, 268] Five guidance documents from Europe,[12, 261] Australasia[251, 252] and India[254] recommend 75 PCI procedures per year for each operator to maintain competence. In addition, three guidance documents also recommend 75 PCI procedures per year but with caveats.[257, 259, 262] The BCIS 2015 recommends 150 procedures per two years, which can include a maximum of 30 interventional diagnostic procedures (including a mix of elective and non-elective patients);[262] the Italian SICI-GISE 2015 recommends a minimum of 75 PCI procedures per year at a

site which performs more than 400 PCI procedures per year;[257] and the Polish Cardiac Society, PTK, 2013 recommends a minimum of 225 PCI procedures should be performed over three years.[259] A 2012 guidance document from the ACCF/SCAI in the US acknowledges the threshold of 75 PCI procedures per year, but they do not endorse it. They state that the 'annual minimum operator interventional procedural volume of 75 cases per year has become an accepted standard for ensuring quality. The value of using an annual threshold of 75 cases per year is limited.'

The CSANZ 2016 guidelines do not give a threshold, but state that it is not ideal for operators performing fewer than 100 procedures per year to operate in centres performing fewer than 400 procedures per year.[253] The Dutch NVVC practice document recommends a minimum of 150 procedures per year, but clarifies that in exceptional cases (for example, long-term illness or pregnancy) experienced operators (more than 1,000 PCIs performed in a lifetime) may temporarily perform fewer than 150 PCIs for one to two years, but a minimum of 500 PCIs must be performed within five years.[258]

The Italian SICI-GISE recommended that new centres should have an experienced interventional cardiologist who has been the first operator in more than 1,000 procedures.[257]

3.3.3.3.2 Primary PCI volume

The recommended minimum operator volume for primary PCI is between 11[11, 178, 251-253, 268] and 30[258] primary PCI procedures per year. The most quoted minimum operator volume for primary PCI is 11 primary PCI procedures per year (n=6). Two of the US guidance documents[178, 268] and all three of the CSANZ guidance documents[251-253] make this recommendation. In addition, the ACCF/AHA/SCAI clinical competence statement from 2013 recommends a minimum of 11 primary procedures and 50 elective PCI procedures per year.[11]

The BCIS recommends a minimum of 20 primary PCI procedures per year, while the Dutch NVVC Society recommends a minimum of 30 primary PCI procedures per year to maintain competency.

Other guidelines based their recommendations for primary PCI on the total number of PCI procedures performed; the Swiss Society of Cardiology recommends operators must perform a minimum of 75 PCI procedures per year as the first operator to maintain competency for primary PCI. A BCIS/BCS guidance document from 2015 recommended a minimum of 50 elective or emergency procedures per year within the emergency primary PCI site and a total workload of at least 120 PCI cases plus up to 30 interventional diagnostic procedures.[262]

3.3.3.3.3 Other recommendations regarding operator volume

Some of the guidance documents had specific recommendations around PCI performed without on-site surgical backup. A 2016 expert consensus statement from the SCAI 2016 recommends that 'Operators should perform at least 50 PCIs/year, including 11 primary PCIs, and the institution should ideally recruit more experienced operators. Less experienced operators should have additional oversight, such as backup support.'[268] An ACCF/SCAI 2012 Task Force on expert consensus documents recommends that operators should perform 100 total PCIs per year, including 18 primary PCIs per year and should not begin to perform PCIs in facilities without on-site surgical cover until they have a lifetime experience of 500 PCIs as the primary operator.[266]

One guideline from the ESC/EACTS 2019 made a specific recommendation that left main artery PCI should be performed by operators with a minimum of 25 left main artery PCI procedures per year.[12]

3.3.3.4 Recommendations for surgical cover at a PCI centre

Eleven guidance documents provided recommendations for surgical cover.[11, 178, 252, 253, 255, 257, 258, 260, 262, 263, 266, 268] All of the guidance documents agree that elective[11, 253, 257] and primary PCI[11, 257] may be considered in hospitals without on-site cardiac surgery provided that there is a clear and documented system in place for the urgent transfer of patients to a facility with cardiovascular surgical support.[11, 178, 252, 253, 255, 257, 260, 262, 263, 266, 268] These systems and protocols must be agreed by all stakeholders including both centres, local networks, commissioners and the ambulance service[262] and should be reviewed annually.[253, 263] Transport protocols should be tested at least once[262] or twice[178] per year and should involve the cath lab and the receiving surgical centre. The CSANZ guidance document noted that the supporting facility should be a high-volume PCI centre with on-site cardiac surgery and should perform all high-risk elective PCIs, but did not define 'high-volume'.[253] In addition, the supporting facility should: agree to accept emergent and non-emergent transfers for additional medical care, cardiac surgery or intervention;[178] be available full time for immediate consultation;[258, 268] assume joint responsibility for training of personnel;[253, 262, 268] and participate in regular case discussion and peer review with the non-surgical centre.[253]

Other recommendations included consideration of equipment and staff necessary for the transport of the patients and should include a transportable intra-aortic balloon counter-pulsation pump (IABP)[178, 252, 262] and available staff to accompany the patient, including an anaesthetist when required.[262] Guidance documents note that patients at high risk of complications (see Table 3.4 Key and Table A.16 for definition) should not undergo elective PCI in a centre without on-site surgery,[178,

[266] and that those with high-grade residual left main or multi-vessel disease and clinical or haemodynamic instability should be urgently transferred to an institution with cardiac surgery after culprit vessel primary PCI.[253]

Once a decision is made that emergency surgery is necessary, the transfer of patients should begin within 30 minutes;[178] allow arrival at the surgical hospital within 60 minutes;[178, 262] allow access to the surgical operating room within 90 minutes;[252, 257] and allow cardiopulmonary bypass to start within 120 minutes.[178, 262]

Recommendations regarding institutional volume and operator volume in centres without on-site surgical backup can be found in the relevant sections above. In general it is recommended that these centres should perform large volumes of interventional procedures and that they should recruit more experienced operators.[253, 257, 266, 268]

3.3.3.5 Recommendations regarding staffing

The recommended minimum number and type of staff required for a PCI procedure or centre varies greatly between guidelines and countries. From the most recent SCAI 2016 guidelines included in the review, minimum staffing levels for a PCI procedure include a primary operator assisted by a trainee or physician extender (such as a certified technologist, physician assistant or nurse); one or two of the staff members should be tableside with an additional two staff circulating and monitoring. A similar recommendation is given by the BCIS 2016 position statement: they recommend a consultant interventional cardiologist and at least four other individuals, three of whom should be allied health professionals and at least two should be able to administer IV drugs.[263] Other guidance documents recommend one or two additional staff (nurse, technician or laboratory technician) assist the interventional cardiologist. [256, 258]

Other recommendations per PCI procedure include, two nurses per lab,[257, 262] one radiographer per lab,[257, 262] one physiologist per lab [262] and a separate professional figure with coordination duties,[257] particularly when there is more than one catheter lab.[262]

For an elective PCI centre, the minimum recommended staffing levels from the CSANZ was a minimum of two interventional cardiologists and an on-call team available to deal with post-procedural complications for at least 24 hours after the last procedure is performed.[253]

Six guidance documents made a recommendation in relation to minimum staffing levels in a primary PCI centre. These recommendations varied from two to four interventional cardiologists,[252] [253, 260, 262] [258] with one guideline recommending a

minimum of either two or three interventional cardiologists depending on whether work is being carried out in a single room, or two rooms at the same time.[257]

The 2013 Japanese Circulation Society guidelines, specifies that one physician with at least five years of cardiovascular practice is required for institutions performing PCI and for those performing PCI with percutaneous transluminal coronary rotational atherectomy, an additional full-time physician who has provided cardiovascular surgery practice for at least five years is required.[255]

Three guidance documents recommend that all interventional cardiologists should participate in an agreed 24/7 primary PCI rota.[252, 253, 263] To ensure sustainability, it is recommended that the rota should include a minimum of six to ten interventional cardiologists,[262] or a minimum of four interventional cardiologists per lab.[257]

The BCIS statement on the development of new PCI services (Appendix 5, Table A.21), recommends three independent operators as a minimum for a PCI centre, but states that a service with only three operators may be difficult to sustain long term and services should plan to increase the number to between four and six depending on workload. For primary PCI services the BCIS statement advises that services are unlikely to be sustainable with fewer than five operators.[250]

3.3.3.6 Recommendations regarding time/distance to treatment

Fifteen of the 22 included guidance documents made recommendations around time or distance to treatment (Table 3.3). This outcome is most often defined as door-to-balloon time, but can be measured in a number of other ways. Door-to-balloon time is usually defined as the time interval between the patient's presentation at the door of the hospital and the initiation of treatment or the first balloon inflation during PCI. Door-to-needle time is usually the time interval between patient presentation at the door of the hospital and insertion of the needle. As discussed in section 2.3.9, time-to-treatment measures are often used as quality indicators.

The recommended door-to-balloon time is most often quoted as less than 90 minutes,[175, 252, 261, 264, 266] but is also stated as less than 60 minutes (excluding cardiogenic shock and out-of-hospital arrest).[263] The Netherlands Cardiac Society (NVVC) 2016 practice document specifies that transport to the intervention centre should be within 30 to 45 minutes of initial paramedic contact.[258] NHS England 2013 guidance document, breaks this down into more specific guidance: 'allowing 20-30 minutes for initial assessment of the patient, and a door-to-balloon time of 30-40 minutes for an expected patient, this allows a travel time to the primary PCI centre of 80-100 minutes.'[261]

Recommendations around alternative treatment pathways are often based on time-

to-treatment, with thrombolysis being recommended if transport time to catheter labs is greater than 90 minutes.[175, 264] This time was listed as 120 minutes in one document,[257] in another when considering non-PCI centre to PCI centre transfer,[264] and in a third when including time to wire crossing.[12] When thrombolysis was the recommended treatment strategy, documents recommended a door-to-needle time of 30 minutes or less[175, 264] in patients arriving via ambulance[258] and 60 minutes or less for patients assessed in the emergency department.[258]

Other guidance documents quote a 'first medical contact'-to-balloon time of 120 mins or less [175, 254, 265] or 90 minutes or less[264] for patients presenting to PCI centres and for direct emergency transfers,[265] or patients with a large amount of myocardium at risk.[254]

There is specific guidance around the establishment of new intervention centres. These centres need to develop a formal partnership with an existing centre[258] and the time and distance these centres are from existing centres needs to be carefully considered.[178, 258]

Adherence to the above time or distance recommendations is dependent on the cath lab and staff being prepared on presentation of the patient for catheterisation. Cardiac cath laboratory staff and interventional cardiologists should arrive within 30 minutes of the STEMI activation call.[178, 257, 258]

For centres without on-site surgical backup, there are specific times stated for the transfer of patients, with some guidelines recommending interim timelines for each step of the transfer. These recommendations range from: 30 minutes for a transport vehicle to be available;[178, 258] within 60 minutes for arrival at the surgical hospital once the need for emergency surgery has been established; and a recommendation that the surgical intervention should begin with 120 minutes[178, 258, 262] (see Table 3.4 and Table A.18 for further details).

Thirty additional guidelines were identified that only discussed time-to-treatment criteria.[212, 216-244] These guidance documents were not quality assessed; a brief overview of the recommendations is provided in Table A.20 in Appendix 5.

3.3.3.7 Recommendations regarding monitoring of standards/KPI

Overall, 19 guidance documents reported on monitoring of standards.[11, 12, 175, 178, 251-253, 257-268] In general, it is recommended that there is careful and complete record keeping,[252, 253] and the collection of comprehensive data including the type of intervention, the appropriateness of the intervention, the process and the outcomes.[252, 262]

A number of the guidance documents recommend a database be established to allow for the recording and monitoring of procedures and outcomes at a local and national level.[252, 253, 257, 258, 260, 262, 268] The 2016 Netherlands Society of Cardiology (NVVC) guidelines recommend that it should contain information such as the indication for the procedure, technique and materials used, fluoroscopy time, duration of procedure, result of the procedure, complications, coronary artery bypass surgery and mortality,[258] while others recommend it should contain information on the structure of the service provision, information on the procedure, the appropriateness of the intervention and the process and outcomes of PCI (in-hospital as well as medium to long-term outcomes).[257, 262]

It is recommended that all cath laboratories submit data to a national or regional registry to allow benchmarking and an ongoing system to track complications.[178, 258, 259, 261, 262, 265-268] It is recommended that the registries should be used to monitor operator/institutional volumes, risk-adjusted outcomes, processes and procedural appropriateness[262, 268] and whether any patient groups are under-represented in the treated population.[261]

A quality assurance (QA) programme should include designated clinicians from each cardiology department to lead the audit process and ensure the necessary infrastructure is in place,[262] support of hospital administrators is essential[11] and it is recommended that a quality committee is set up.[11, 268] The function of a QA programme should be to review the quality and outcomes of the entire programme,[11, 251, 252, 264] benchmarking,[178] monitoring the procedures and outcomes of individual operators,[11, 262, 266] risk-adjustment based on patient characteristics and demographics[11, 268] and providing peer review auditing of individual and peer review results.[251, 253, 268]

There should be regular team meetings and case reviews to review outcomes and quality improvement data.[178, 251, 252, 258, 262] It is also recommended that operators and PCI centres be provided with a breakdown of their own PCI activity, including a risk-adjusted outcome analysis and provide a clinical data set that allows for national comparison of interventional techniques and comparative audit.[261, 262]

3.3.3.7.1 Key performance and quality indicators (KPI)

There were numerous quality indicators (QIs) and KPIs recommended in the guidance documents. An overview can be found in Table 3.4. These KPIs fall broadly into eight categories:

- Pre-interventional KPIs which include adherence to guideline recommended pre-treatment protocols [12, 266] and the percentage of direct referrals from the ambulance service.[261]

- Interventional technique KPIs which include procedural success,[12, 266] access route,[12] percentage treated with drug eluting stents,[12] proportion of eligible patients receiving reperfusion therapy[178, 264] and proportion of patients who do not undergo acute catheterisation because of misdiagnosis.[178, 264]
- Peri-interventional outcome rates including death,[12, 178, 260, 266] peri-procedural MI, stroke, contrast-induced nephropathy, major bleeding, respiratory arrest, nerve injury, radiation injuries, perforation of heart vessel with sequelae and emergency cardiovascular surgery.[12, 266]
- Discharge KPIs including the proportion discharged on antiplatelet medication,[12] high-dose lipid lowering medication,[12] and the percentage referred to an early cardiac rehabilitation/secondary prevention programme on discharge.[175]
- Follow-up KPIs include readmission rates, 30-day and one-year mortality rates, unplanned and repeat revascularisation within one year, stent thrombosis and major bleeding.[12]
- There are a number of different timing QIs recommended including door-to-balloon time,[175, 178, 263, 264, 266] door-to-first-device time,[178] 'first medical contact'-to-balloon inflation time,[175, 264] call-to-balloon time,[261] door-to-needle time,[175, 264] time to first ECG,[264] time from arrival at the emergency department to transfer to a PCI capable centre,[264] as well as KPIs around the length of stay in hospital.[175]
- There are also KPIs around service and financial outcomes such as the procedural costs[266] and satisfaction surveys.[266]

Table 3.4: Organisational and service specification recommendations for centres providing PCI

Criteria regarding	Recommendation(s)	Organisations
Institutional facilities	**All PCI facilities:**	
	▪ At least one cardiac catheterisation laboratory. A second laboratory is ideal, however a non-cardiac radiological facility used for general radiology backup or a high resolution portable fluoroscopy unit with a small image intensifier is the minimum requirement.	▪ BCIS and BCS (2015)
	▪ High resolution digital imaging capacity, real-time transferring and archiving of images equipment.	▪ ACCF/AHA/SCAI (2013), BCIS and BCS (2015), CSANZ 2014b, PTK (2013), SCAI/ACC/AHA (2014), SICI-GISE (2015)
	▪ Physiological assessment facilities which allow accurate monitoring and recording of ECG lead configurations, pressure, heart rate and oxygen saturation.	▪ ACCF/AHA/SCAI (2013), BCIS and BCS (2015), CSANZ 2016, DGK (2015), PTK (2013), SCAI/ACC/AHA (2014), SICI-GISE (2015), SSC (2014)
	▪ Radiation protection, monitoring and recording equipment.	▪ BCIS and BCS (2015), SICI-GISE (2015), NVVC (2016)
	▪ New institutions must have an ionisation chamber for measuring and recording dose-area product.	▪ SICI-GISE (2015)
	▪ Cardiac laboratory equipment, such as IABP, an anaesthetic machine and facilities for monitoring anticoagulation.	▪ ACCF/AHA/SCAI (2013), BCIS and BCS (2015), BCIS (2016), CSANZ 2014b, CSANZ 2016, DGK (2015), NHS England (2013), NVVC (2016), PTK (2013), SICI-GISE (2015)
	▪ Full resuscitation facilities including a defibrillator.	▪ BCIS and BCS (2015), BCIS (2016), CSANZ 2014b, DGK (2015), NHS England (2013), PTK (2013), SICI-GISE (2015), SSC (2014)
	▪ Additional imaging or procedural tools, such as flow and pressure wires, IVUS, optical coherence tomography.	▪ ACCF/AHA/SCAI (2013), BCIS and BCS (2015), NVVC (2016), PTK (2013), SCAI/ACC/AHA (2014), SICI-GISE (2015)
	▪ Disposable angioplasty equipment, such as antithrombotic medications, guide catheters, guide wires, balloons and stents.	▪ BCIS and BCS (2015), NVVC (2016), SCAI/ACC/AHA (2014), SICI-GISE (2015)

Criteria regarding	Recommendation(s)	Organisations
	▪ A ventilator.	▪ DGK (2015), PTK (2013), SICI-GISE (2015)
	▪ Access to non-invasive positive pressure ventilation (CPAP).	▪ BCIS (2016)
	▪ Adequate cardiac catheterisation laboratory specifications:	▪ PTK (2013)
	– One or more haemodynamic-angiographic rooms of not less than 32m^2 with 2 technical compartments of 12m^2 and a control room of 7m^2.	– SICI-GISE (2015)
	– Other premises for preparation and storage of materials, washing and dressing of personnel, and decontamination and cleaning of medical devices.	– DGK (2015), SICI-GISE (2015)
	– Enough for ventilated patients and possible resuscitation measures (usually >40m^2).	– DGK (2015)
	– At least one surgical light with sterile cover and sufficient brightness (>20,000 lux).	– DGK (2015)
	– An uninterruptible power supply or at least an emergency generator	– DGK (2015), SICI-GISE (2015)
	– A refrigerator for medicines.	– DGK (2015)
	▪ Systems for credentialing, governance, data gathering, and quality assessment.	▪ ACCF/AHA/SCAI (2013), ACCF/SCAI (2012)
	▪ On-site ICU.	▪ CSANZ (2016)
	– Or an intermediate care unit (requirements outlined in Table A.13 in Appendix 4).	– SSC (2014)
	– High-risk PCI procedures (such as for left main coronary artery disease or complex CTO) should only performed at centres that have access to circulatory support and intensive care treatment.	– ESC/EACTS (2019)
	▪ Legal provisions on the prevention of accidents.	▪ SICI-GISE (2015)
	▪ Equipment must be available and in good operating order/serviced regularly.	▪ ACCF/AHA/SCAI (2013), DGK (2015)
	▪ New centres must comply with all requirements within 3 years.	▪ NVVC (2016)
	▪ An on-call team available to deal with post-procedural complications for at least 24 hours after the last procedure is performed.	▪ CSANZ (2016)
	Primary PCI centres:	
	▪ Two cardiac catheterisation laboratories.	▪ BCIS (2016), CCN (2013), HSE/RCPI (2012), NHS England (2013), NVVC (2016)

Criteria regarding	Recommendation(s)	Organisations
	▪ Availability 24 hours per day, 7 days per week.	▪ ACCF/SCAI (2012), BCIS (2016), CCN (2013) ESC/EACTS (2019), HSE/RCPI (2012), NHS England (2013), NVVC (2016), PTK (2013), SCAI/ACC/AHA (2014), SICI-GISE (2015), SSC (2014)
	– New centres only need to provide services during regular operational hours, but must have arrangements with a supervising centre which can provide treatment outside these hours.	– NVVC (2016), PTK (2013)
	– Once there is sufficient infrastructure (workforce and clinical services) to ensure that procedures can be performed safely outside routine working hours and sufficient appropriately trained interventional cardiologists.	– CSANZ (2014b), CSANZ (2016)
	▪ An extensive support system of specifically trained laboratory personnel:	▪ PTK (2013)
	– Interventional cardiologists, anaesthesiologists, intensive care physicians, nurses, radiographers and technicians.	– HSE/RCPI (2012), NHS England (2013), SICI-GISE (2015)
	– Cardiothoracic surgical, respiratory, and anaesthesia services.	– ACCF/AHA/SCAI (2013)
	▪ A network of services organised in collaboration with emergency/ambulance services, which:	
	– Contains a PCI Centre in partnership with all hospitals which treat STEMI patients ('hub and spoke' model).	– CCN (2013)
	– Ideally includes an 'in-field activation' programme to minimise treatment delays.	– CSANZ (2014b)
	– Involves pre-hospital management based on regional networks and all EMS, emergency departments, coronary care units, and catheterisation laboratories having written updated STEMI management protocols, which are preferably shared within the geographical networks.	– ESC/EACTS (2019)
	– Ensures pre-hospital triage with 12 lead ECG application and transmission/interpretation is available via trained and equipped EMS.	– HSE/RCPI (2012)
	– Includes a cardiac surgery, vascular surgery, stroke unit and nephrology department, set up in a 'hub and spoke' model.	– SICI-GISE (2015)
	▪ No refusal policy.	▪ CCN (2013), HSE/RCPI (2012)
	▪ Inter-hospital agreements for the initial acceptance of the STEMI patients and for the repatriation of these patients after treatment.	▪ CCN (2013)

Criteria regarding	Recommendation(s)	Organisations
	▪ A Coronary Care Unit/Intensive Care Unit with adequate step down beds.	▪ HSE/RCPI (2012), NHS England (2013), PTK (2013), SICI-GISE (2015), SSC (2014)
	▪ Centres should have contingencies to deal with rare occasions when the service has to be temporarily withdrawn (adverse weather, major power failure, etc.).	▪ NHS England (2013)
	▪ Facilities to allow access to cardiac rehabilitation and secondary prevention prior to discharge.	▪ HSE/RCPI (2012)
	▪ Dedicated call service and point/s for ECG reception.	▪ BCIS (2016), HSE/RCPI (2012)
	▪ Patients should bypass the emergency department and be transferred directly to the catheterisation laboratory.	▪ BCIS (2016), CCN (2013), ESC/EACTS (2019)
	▪ Full support and commitment from hospital administration.	▪ CSANZ (2014b)
	▪ Routine primary PCI should only be performed after an elective PCI programme has been established and shown to perform with acceptable morbidity and mortality. Institutions should participate in 3-6 month period of implementation, during which time development of a formalized primary PCI programme is instituted that includes establishment of standards, training of staff, logistic development and creation of a quality-assessment and error management system.	▪ CSANZ (2014b), CSANZ (2016)
	PCI centres without on-site surgical cover:	
	▪ Clear and documented systems for the urgent transfer of patients to a facility with cardiovascular support.	▪ ACCF/SCAI (2012)
	– For centres during the 'Start-up' phase.	– PTK (2013)
Institutional volume	**Total PCI volume:**	
	▪ Minimum 400 procedures per year.	▪ BCIS and BCS (2015), CCS (2015), SICI-GISE (2015)
	– Institutions performing <400 procedures per year can be considered tolerable when located in geographically remote areas that present considerable difficulties with regard to the rapid transfer of patients or in the start-up phase.	– SICI-GISE (2015)
	– Institutions performing <400 procedures per year must hold conferences with a more experienced partnering institution.	– ACCF/SCAI (2012)
	– For centres performing PCI for acute coronary syndromes.	– ESC/EACTS (2019)

Criteria regarding	Recommendation(s)	Organisations
	– It should be considered that institutions with annual volumes of <400 PCIs collaborate in networks with higher-volume institutions (>400 PCIs per year), with shared written protocols and exchange of operators and support staff.	– ESC/EACTS (2019)
	▪ Not ideal for centres performing <400 procedures per year to have operators who perform <100 procedures per year.	▪ CSANZ (2016)
	▪ Minimum 200 procedures per year.	▪ ACCF/AHA/SCAI (2013), CSANZ (2014b), SCAI (2016), SCAI/ACC/AHA (2014), SSC (2014)
	– Institutions performing <200 cases per year must have stringent systems and process protocols with close monitoring of clinical outcomes and additional strategies that promote adequate operator and catheterisation laboratory staff experience through collaborative relationships with larger-volume facilities.	– ACCF/AHA/SCAI (2013)
	– With an ideal minimum of 400 procedures per year.	– CSANZ (2014a)
	– In addition to a minimum of 30 cases of open-heart surgery, coronary or aortic bypass surgery annually.	– JCS (2013)
	– For centres performing PCI for stable coronary artery disease.	– ESC/EACTS (2019)
	▪ Minimum 600 procedures per year.	▪ NVVC (2016)
	– New centres: minimum of 400 procedures per year in second year, 600 procedures per year from third year.	– NVVC (2016)
	– Supervisory centres: minimum 800 procedures per year.	– NVVC (2016)
	▪ Minimum number of procedures for:	▪ PTK (2013)
	– Start-up invasive cardiology laboratory is >240 per year.	– PTK (2013)
	– Advanced invasive cardiology laboratory is >500 per year.	– PTK (2013)
	– Reference invasive cardiology laboratory is >700 per year.	– PTK (2013)
	▪ No specific threshold.	▪ ACC/AHA/SCAI/AMA (2014)
	Primary PCI volume:	
	▪ Minimum 100 primary PCI procedures per year.	▪ BCIS and BCS (2015), NHS England (2013)
	▪ Centres performing <300 primary PCIs/year should consider annually whether a Network approach which rationalises the number of adjacent primary PCI centres would be a more appropriate model of care.	▪ BCIS and BCS (2015)

Criteria regarding	Recommendation(s)	Organisations
	▪ Minimum 36 primary PCI per year.	▪ API (2011), CSANZ (2014a), CSANZ (2014b), CSANZ (2016), SCAI (2016), SCAI/ACC/AHA (2014)
	– Ideally, >200 elective PCI and >36 primary PCI.	– ACCF/AHA/SCAI (2013)
	▪ Minimum 300 elective PCI procedures per year.	▪ SSC (2014)
	▪ Minimum 150 primary PCI procedures per year unless there is extreme geographical isolation to justify a lower volume service.	▪ BCIS (2016)
	– If PPCI centres are consistently performing <150 PPCI procedures per year, annual review to consider whether local transfer times would support coalescing with adjacent sites.	– BCIS (2016)
Operator volume	**Total PCI volume:**	
	▪ Minimum 75 procedures per year.	▪ API (2011), CSANZ (2014a), CSANZ (2014b), ESC/EACTS (2019), NHS England (2013)
	– Averaged over 2 years (i.e. 150 procedures per 2 years) which can include up to a maximum of 30 interventional diagnostic procedures (including a mix of elective and non-elective patients).	– BCIS and BCS (2015)
	– At sites which perform more than 400 PCI per year.	– SICI-GISE (2015)
	– Averaged over 3 years (i.e. 225 procedures over 3 years).	– PTK (2013)
	– Noted previous guideline recommendation of 75 cases per year but discussed how this was of limited value.	– ACCF/SCAI (2012)
	▪ Operators absent from practice for less than 6 months: no additional training required.	▪ BCIS and BCS (2015)
	▪ Operators absent for between 6 months and 2 years: a buddy system for 20–50 PCI procedures (proportional to the period of absence).	▪ BCIS and BCS (2015)
	▪ Operators who have fully trained but have not undertaken any procedures for 2 years or more: should perform at least 75 PCI procedures with a mentor.	▪ BCIS and BCS (2015)
	▪ New centres should have an experienced interventional cardiologist who has been first operator for >1000 procedures.	▪ SICI-GISE (2015)
	▪ Minimum of 50 procedures per year.	▪ SSC (2014)
	– averaged over a 2-year period (i.e. 100 procedures per 2 years).	– ACCF/AHA/SCAI (2013), SCAI (2016), SCAI/ACC/AHA (2014)
	▪ No threshold.	▪ ACC/AHA/SCAI/AMA (2014)

Criteria regarding	Recommendation(s)	Organisations
	▪ Minimum 150 procedures per year.	▪ NVVC (2016)
	– In exceptional cases (long-term illness, pregnancy, study leave) or experienced operators (>1000 PCIs) may temporarily perform less than 150 therapeutic PCIs for 1-2 years, but a minimum of 500 therapeutic PCIs must be performed within 5 years.	– NVVC (2016)
	▪ Not ideal for operators performing <100 procedures per year to operate in centres performing <400 procedures per year.	▪ CSANZ (2016)
	Primary PCI volume:	
	▪ Minimum 50 procedures per year within the primary PCI site and a total workload of 120 PCI procedures and up to 30 interventional diagnostic procedures.	▪ BCIS and BCS (2015)
	▪ Minimum 11 PPCI procedures per year.	▪ CSANZ (2014a), CSANZ (2014b), CSANZ (2016), SCAI (2016), SCAI/ACC/AHA (2014)
	– And 50 elective PCI procedures per year.	– ACCF/AHA/SCAI (2013)
	▪ Minimum 75 procedures per year.	▪ SSC (2014)
	▪ Minimum 20 primary PCI procedures per year.	▪ BCIS (2016)
	▪ Minimum of 30 primary PCI procedures per year.	▪ NVVC (2016)
	Left main PCI:	
	▪ Minimum 25 left main PCI procedures per year.	▪ ESC/EACTS (2019)
	PCI without on-site surgical cover:	
	▪ Operators should perform 100 total PCIs per year, including 18 primary PCIs per year.	▪ ACCF/SCAI (2012)
	▪ Operators should not begin performing PCI in facilities without on-site surgical cover until they have a lifetime experience of 500 PCIs as primary operator.	▪ ACCF/SCAI (2012)
	▪ Operators should perform at least 50 PCIs/year, including 11 primary PCIs, and the institution should ideally recruit more experienced operators. Less experienced operators should have additional oversight, such as backup support.	▪ SCAI (2016)
Surgical cover	▪ Provided that appropriate planning for programme development has been accomplished:	

Criteria regarding	Recommendation(s)	Organisations
	– Elective PCI might be considered in hospitals without on-site cardiac surgery.	– ACCF/AHA/SCAI (2013), CSANZ (2016), NVVC (2016), SICI-GISE (2015)
	– If they can provide primary PCI coverage for more than just daytime and weekday hours.	– ACCF/SCAI (2012)
	– Primary PCI might be considered in hospitals without on-site cardiac surgery.	– ACCF/AHA/SCAI (2013), NVVC (2016), SICI-GISE (2015)
	▪ PCI centres without on-site surgical cover should have clear and documented systems for the urgent transfer of patients to a facility with cardiovascular surgical support.	▪ ACCF/AHA/SCAI (2013), ACCF/SCAI (2012), BCIS (2016), BCIS and BCS (2015), CSANZ (2014b), CSANZ (2016), JCS (2013), NVVC (2016), SCAI (2016), SCAI/ACC/AHA (2014), SICI-GISE (2015), SSC (2014)
	– These should be annually reviewed.	– BCIS (2016), CSANZ (2016)
	– The supporting facility should be a high-volume PCI centre.	– CSANZ (2016)
	– The supporting facility must agree to accept emergent and non-emergent transfers for additional medical care, cardiac surgery or intervention.	– SCAI/ACC/AHA (2014)
	– The supporting facility should perform the high risk elective PCIs.†	– CSANZ (2016)
	– The supporting facility should assume joint responsibility for training of personnel.	– BCIS and BCS (2015), CSANZ 2016. SCAI (2016)
	– The supporting facility should participate in regular case discussion and peer review with the non-surgical centre.	– CSANZ (2016)
	– The supporting facility should be available full time for immediate consultation.	– NVVC (2016), SCAI (2016)
	– The protocol must be agreed by all stakeholders, including both centres, local networks, commissioners, and the ambulance service.	– BCIS and BCS (2015)
	▪ A good working relationship with the cardiac surgical team in the surgical centre is essential for all non-surgical PCI centres.	▪ BCIS and BCS (2015), CSANZ (2016)
	– For rural and regional centres without cardiac surgery ideally the Director should be cross accredited at this referral hospital and perform procedures at this hospital on a regular basis.	– CSANZ (2016)
	▪ Necessary equipment should be considered, including:	
	– A transportable intra-aortic balloon counter-pulsation pump (IABP).	– BCIS and BCS (2015), CSANZ (2014b), SCAI/ACC/AHA (2014)

Criteria regarding	Recommendation(s)	Organisations
	– The availability of staff to accompany the patient, including an anaesthetist when required.	– BCIS and BCS (2015)
	▪ After the decision to declare the need for emergency surgery, transfer of patients should:	
	– Begin within 30 minutes.	– SCAI/ACC/AHA (2014)
	– Allow arrival at the surgical hospital within 60 minutes.	– BCIS and BCS (2015), SCAI/ACC/AHA (2014)
	– Allow access to the surgical operating room within 90 minutes.	– CSANZ (2014b), SICI-GISE (2015)
	– Allow the ability to start cardiopulmonary bypass within 120 minutes.	– BCIS and BCS (2015), SCAI/ACC/AHA (2014)
	▪ The feasibility of ambulance transfer of the IABP should be tested to confirm it can be achieved within the required 120 min timeline.	▪ BCIS and BCS (2015)
	▪ Transport protocols should be tested:	
	– A minimum of 2 times per year, involving both the referring and receiving facility.	– SCAI/ACC/AHA (2014)
	– Annually with a virtual run (without the requirement for actual 'blue light' driving), involving the catheter lab to surgical centre transfer with IABP.	– BCIS and BCS (2015)
	▪ When considering PCI volume:	
	– The institution should perform large volumes of interventional procedures.	– SICI-GISE (2015)
	– The institution should ideally recruit more experienced operators and less experienced operators should have additional oversight, such as backup support.	– SCAI (2016)
	– Operators performing PCI without on-site surgery should:	
	▪ Perform 100 total PCIs per year, including 18 primary PCIs per year.	▪ ACCF/SCAI (2012)
	▪ Perform >75 elective PCI procedures per year and >11 primary PCI cases per year.	▪ CSANZ (2014b), CSANZ (2016)
	▪ Have a lifetime experience of 500 PCIs as primary operator before beginning to perform PCIs at such centres.	▪ ACCF/SCAI (2012)
	– It is not ideal that low-volume operators (<100 PCIs per year) perform PCIs in low-volume centres (centre performing <400 PCIs per year).	– CSANZ (2016)
	– New PCI services (especially those in rural and regional centres more than 1 hour travel time from cardiac surgery) should be initially supervised by an experienced operator (> 1000 PCI procedures), who should be present during cases and mentor less experienced operators.	– CSANZ (2016), SICI-GISE (2015)

Criteria regarding	Recommendation(s)	Organisations
	– Institutions performing fewer than 200 procedures annually, unless in a region underserved because of geography, should strongly consider whether or not it should continue to offer this service.	– ACCF/AHA/SCAI (2013)
	– For primary PCI, institutions should perform >200 overall PCI cases and >36 primary PCI procedures per year.	– CSANZ (2014b), CSANZ (2016)
	▪ Hospitals should accredit cardiologists individually to perform PCIs.	▪ CSANZ (2016)
	▪ Centres should:	
	– Participate in national registries.	– SCAI (2016)
	– Routinely use risk adjustment tools.	– SCAI (2016)
	– Have coronary care facilities and an ICU.	– CSANZ (2016)
	▪ Centres should have:	
	– A minimum of 3 hemodynamists.	– SICI-GISE (2015)
	– Ideally a minimum of 2 appropriately trained interventional cardiologists.	– CSANZ (2016)
	– A minimum of one full-time physician who has provided cardiovascular surgery practice for at least 5 years.	– JCS (2013)
	– An on call team available for at least 24 hours following the last case to deal with any post-procedural complications.	– CSANZ (2016)
	▪ Centres should first develop a diagnostic coronary angiography service for 12 months and demonstrate acceptable morbidity and mortality rates. Consideration may be given to abbreviating this period, particularly in circumstances where a highly experienced operator (performed >1,000 PCI cases) is developing the new interventional service and is supported by appropriately skilled cardiac catheterisation staff.	▪ CSANZ (2016)
	▪ Case selection must be rigorous	
	– High-risk patients or those with high-risk lesions should not undergo elective PCI in a facility without on-site surgery.†	– ACCF/SCAI (2012), SCAI/ACC/AHA (2014)
	▪ If more than 1 hour travel time from cardiac surgery.	▪ CSANZ (2016)
	– Discretion should be exercised when assessing haemodynamically stable patients with complex infarct related lesions that have TIMI 3 flow.	– CSANZ (2014b)
	– Urgent transfer to institution with cardiac surgery of patients with high-grade residual left main or multi-vessel disease and clinical or haemodynamic instability after culprit vessel primary PCI.	– CSANZ (2014b)

Criteria regarding	Recommendation(s)	Organisations
Staffing numbers	▪ Minimum staffing levels for a PCI procedure:	
	– A consultant interventional cardiologist and at least 4 other individuals, including at least 3 allied health professionals of whom 2 should be able to administer IV drugs.	– BCIS (2016)
	– A primary operator assisted by a physician trainee and/or physician extenders (e.g. certified technologist, physician assistant, or nurse). Typically, 1–2 staff are tableside, with an additional 2 staff serving in 'circulating' and 'monitoring/recording' roles.	– SCAI (2016)
	– At least 1 interventional cardiologist and 2 additional members of an intervention team (a nurse and an additional nurse, technician or laboratory technician).	– NVVC (2016)
	– An interventional cardiologist and a nursing/medical-technical assistant.	– DGK (2015)
	– 2 nurses per lab.	– BCIS and BCS (2015), SICI-GISE (2015)
	▪ And one floater nurse.	▪ BCIS and BCS (2015)
	– 1 radiographer per lab.	– BCIS and BCS (2015), SICI-GISE (2015)
	– 1 physiologist per lab.	– BCIS and BCS (2015)
	– At least 1 technologist (and/or physician) skilled in radiographic and angiographic imaging techniques.	– ACCF/SCAI (2012)
	– In complex cases and procedures, the presence of a second physician may be needed for optimal care.	– ACCF/SCAI (2012)
	– A separate professional figure with coordination functions.	– SICI-GISE (2015)
	▪ Should be considered for units with more than one catheter lab.	▪ BCIS and BCS (2015)
	▪ Minimum staffing levels for a primary PCI centre:	
	– 2 interventional cardiologists.	– CSANZ (2014b)
	▪ If work carried out in a single room.	▪ SICI-GISE (2015)
	– 3 interventional cardiologists.	– BCIS and BCS (2015), CSANZ (2016), SSC (2014)
	▪ If the work is carried out contemporarily in 2 rooms.	▪ SICI-GISE (2015)
	▪ For a 9-5 centre.	▪ HSE/RCPI (2012)
	– 4 interventional cardiologists.	– NVVC (2016)

Criteria regarding	Recommendation(s)	Organisations
	▪ New institutions require at least 2 interventional cardiologists. After 2 years, at least 3 interventional cardiologists, and after 3 years, at least 4 interventional cardiologists.	▪ NVVC (2016)
	– At least 1 technologist, preferably a certified radiological technologist, skilled in radiographic and angiographic imaging principles and techniques.	– ACCF/SCAI (2012)
	– At least 1 technologist proficient in equipment use, maintenance, and general troubleshooting.	– ACCF/SCAI (2012)
	▪ Minimum staffing levels for an elective PCI centre:	
	– 2 interventional cardiologists.	– CSANZ (2016)
	– An on-call team available to deal with post-procedural complications for at least 24 hours after the last procedure is performed.	– CSANZ (2016)
	▪ Minimum staffing levels for institutions providing PTCA (PCI; percutaneous coronary angioplasty, percutaneous coronary thrombectomy, and percutaneous coronary stenting): 1 physician who has provided cardiovascular practice for at least 5 years.	▪ JCS (2013)
	▪ Minimum staffing levels for institutions providing percutaneous coronary angioplasty using PTCRA (Rotablator): 1 physician who has provided cardiovascular practice for at least 5 years and 1 full-time physician who has provided cardiovascular surgery practice for at least 5 years.	▪ JCS (2013)
	▪ Some centres have used joint cover arrangements with neighbouring centres to facilitate the initiation of the service. This arrangement should be regarded as temporary (<2years).	▪ BCIS and BCS (2015)
	▪ All interventional cardiologists should participate in an agreed 24/7 primary PCI rota.	▪ BCIS (2016), CSANZ (2014b), CSANZ (2016)
	– To be sustainable this should include:	
	▪ A minimum of 6 interventional cardiologists and ideally 10.	▪ BCIS and BCS (2015)
	▪ A minimum of 4 interventional cardiologists per lab.	▪ SICI-GISE (2015)
	▪ A minimum roster of 1:5 interventional cardiologists.	▪ HSE/RCPI (2012)
	▪ A maximum frequency of on-call rota for any individual no more frequent than 1:6.	▪ BCIS (2016)
	▪ With less staff on call and on weekends, a procedure for further assistance in emergencies should be established.	▪ DGK (2015)

Criteria regarding	Recommendation(s)	Organisations
	▪ A catheter lab 'crash team' should include a senior anaesthetist. This team should have sufficient flexibility in their duties to remain within the catheter lab and allow the revascularisation procedure to be completed.	▪ BCIS (2016)
	▪ All cardiac catheter laboratories should have a Director of Laboratory who is experienced in interventional procedures.	▪ ACCF/SCAI (2012), CSANZ (2016)
	– At least 5 years of cardiac catheterisation experience. Directors that have performed <500 PCI cases should have a QA system in place until >500 PCI cases have been performed.	– ACCF/SCAI (2012)
	▪ A technician with expert computer skills is a very valuable addition to the team to assist with the handling of image transfer methods and archival storage devices, image compression, and to maintain the digital libraries.	▪ ACCF/SCAI (2012)
	▪ On occasion, additional administrative personnel may assist in the optimal functioning of the cardiac catheterisation laboratory. Such personnel may include a dedicated case manager, scheduler, inventory manager and related staff, compliance monitor, and database or administrative staff for CQI and QA.	▪ ACCF/SCAI (2012)
	▪ A nurse providing moderate sedation during the procedure must have no other responsibilities that would compromise continuous patient assessment. In cases where there is concern for using more than moderate sedation, an anaesthesia provider should be present, and policies should be drafted that are consistent with hospital credentialing and state guidelines.	▪ ACCF/SCAI (2012), SCAI (2016)
	▪ Nursing and technical catheterisation staff must be experienced in managing acutely unwell patients and be adept in haemodynamic monitoring, temporary pacemaker operation and IABP management.	▪ CSANZ (2014b)
Time or distance to treatment	**Thrombolysis/fibrinolysis** ▪ Thrombolysis/fibrinolysis should be the recommended strategy if transport times to the cath lab are greater than:	
	– 90 minutes	– CCN (2013), HSE/RCPI (2012)
	– 120 minutes	– SICI-GISE (2015)
	▪ For non-PCI site to PCI centre transfer	▪ CCN (2013)
	▪ Including time to wire crossing	▪ ESC/EACTS (2019)
	▪ Door-to-needle ≤30 minutes	▪ CCN (2013), HSE/RCPI (2012)
	– For patients arriving by ambulance.	– NVVC (2016)

Criteria regarding	Recommendation(s)	Organisations
	▪ Door-to-needle ≤60 minutes for patients assessed in the emergency room.	▪ NVVC (2016)
	Primary PCI	
	▪ Start primary PCI as soon as possible but preferably within 60 minutes from the initial call.	▪ SSC (2014)
	▪ Call-to-balloon time <150 minutes.	▪ NHS England (2013)
	– In ≥75% of patients (excluding cardiogenic shock and out-of-hospital arrest).	– BCIS (2016)
	▪ First medical contact to ECG and diagnosis <10 min.	▪ ESC/EACTS (2019)
	▪ STEMI diagnosis to primary PCI (wire crossing) in transferred patients <90 min.	▪ ESC/EACTS (2019)
	▪ STEMI diagnosis to wire crossing in patients presenting at primary PCI hospitals <60 mins.	▪ ESC/EACTS (2019)
	▪ First medical contact to balloon time ≤120 mins	▪ API (2011), HSE/RCPI (2012)
	– For patients transferred from non-PCI centres and for direct emergency medical services transfers in provinces with few cath labs. The goal should be to meet the target in at least 75% of cases	– CCS (2015)
	▪ First medical contact to balloon time ≤90 minutes	▪ CCN (2013)
	– For patients presenting early with a large amount of myocardium at risk.	– API (2011)
	– For patients presenting to PCI centres and for direct emergency medical services transfers for provinces with easy access to cath labs. The goal should be to meet the target in at least 75% of cases	– CCS (2015)
	▪ Door-to-balloon time <90 minutes.	▪ ACCF/SCAI (2012), CSANZ (2014b), HSE/RCPI (2012), NHS England (2013)
	▪ Door-to-balloon time <60 minutes in ≥75% of patients (excluding cardiogenic shock and out-of-hospital arrest).	▪ BCIS (2016)
	▪ Allowing 20-30 minutes for initial assessment of the patient, and a door-to-balloon time of 30-40 minutes for an expected patient, this allows a travel time to the primary PCI centre of 80-100 minutes.	▪ NHS England (2013)
	▪ Transport to an intervention centre should be within 30-45 minutes of initial paramedical contact.	▪ NVVC (2016)
	– A maximum drive time of 45 minutes, with some discretion to reflect local circumstances and the patient's condition	– CCN (2013)

Criteria regarding	Recommendation(s)	Organisations
	▪ The cardiac catheterisation laboratory staff and interventional cardiologist should arrive within 30 minutes of a STEMI activation call.	▪ NVVC (2016), SCAI/ACC/AHA (2014), SICI-GISE (2015)
	– Facilities should have a plan for triage and treatment of simultaneous presentation of STEMI patients.	– SCAI/ACC/AHA (2014)
	▪ Geographical isolation:	
	– In some isolated areas a case volume >300 primary PCI patients per annum may be impractical and a minimum of 100 primary PCI procedures per annum is more practical.	– BCIS and BCS (2015)
	– In non-metropolitan centres with adequate facilities, a high-volume operator (experience > 1,000 PCI cases, including undertaking >11 primary PCI per year) in an established unit with experience in elective PCI, may perform primary PCI without a dedicated 24 hours-per-day, 365-days-per-year program	– CSANZ (2014b)
	Requirements for new intervention centres:	
	▪ Acceptance of the need for new centres should be motivated from a geographical point of view.	▪ NVVC (2016)
	– The development of PCI facilities within a 30-minute emergency transfer time to an established facility is strongly discouraged.	– SCAI/ACC/AHA (2014)
	▪ Centres should start a formal partnership with an existing intervention centre. The new centre should not be more than 30-45 minutes away by ambulance.	▪ NVVC (2016)
	▪ The cardiac catheterisation laboratory should be operational within 30 minutes announcement of an acute process.	▪ NVVC (2016)
	▪ New PCI services, especially those in rural and regional centres more than 1 hour travel time from cardiac surgery, should be initially supervised by an experienced operator (experience of more than 1,000 PCI cases), who should be present during cases and mentor less experienced operators.	▪ CSANZ (2016)
	▪ New PCI services, especially those in rural and regional centres more than 1 hour travel time from cardiac surgery, should be initially supervised by an experienced operator (experience of >1,000 PCI cases), who should be present during cases and mentor less experienced operators.	▪ CSANZ (2016)
	Centres without on-site surgical cover:	

Criteria regarding	Recommendation(s)	Organisations
	▪ Formalised protocols with the closest facility offering cardiac surgery are mandatory, aimed at ensuring timely access to the operating room within 90 minutes of the occurrence of the need for surgery.	▪ SICI-GISE (2015)
	▪ A transport vehicle should be available to begin transport within 30 minutes.	▪ SCAI/ACC/AHA (2014)
	▪ Arrival at the surgical hospital within 60 minutes of the decision of the need for emergency surgery.	▪ BCIS and BCS (2015), SCAI/ACC/AHA (2014)
	▪ Surgical intervention should begin within 120 minutes.	▪ BCIS and BCS (2015), SCAI/ACC/AHA (2014)
	▪ Rural and regional centres more than 1 hour travel time from cardiac surgery, should not perform elective, high-risk PCIs.†	▪ CSANZ (2016)
Monitoring of standards	▪ All PCI centres are expected to have a local database to collect comprehensive and accurate data that relate to the interventional treatment they provide for their patients.	▪ BCIS and BCS (2015), CSANZ (2014b), CSANZ (2016), SSC (2014)
	– Includes information pertaining to the structure of service provision, the appropriateness of intervention, and the process and outcomes of PCI.	– BCIS and BCS (2015)
	– Includes information on procedures, materials used, and in-hospital and medium-long term outcome data.	– SICI-GISE (2015)
	– Includes information on the indication of the procedure, technique and materials used, fluoroscopy time, duration of the procedure (from puncturing to removal of the guiding catheter), result of the procedure, complications, coronary artery bypass surgery and mortality. Preferably there is also information about hospital discharge.	– NVVC (2016)
	▪ All cardiac catheterisation laboratories should submit data to a national registry to benchmark their results and provide an ongoing system for tracking complications.	▪ BCIS and BCS (2015), NHS England (2013), NVVC (2016), SCAI/ACC/AHA (2014)
	– Reporting monthly.	– PTK (2013)
	– Reporting annually.	– CCS (2015), SSC (2014)
	– Registries may be regional or national.	– ACC/AHA/SCAI/AMA (2014), ACCF/SCAI (2012), SCAI (2016)
	▪ Registries should be utilised to monitor operator/institutional volumes, risk-adjusted outcomes, processes, and procedural appropriateness	▪ BCIS and BCS (2015), SCAI (2016)

Criteria regarding	Recommendation(s)	Organisations
	– And whether any patient groups are under-represented in their treated population.	– NHS England (2013)
	– Should be reported as sequential trend analysis by year and median or the 25th and 75th percentiles for the selected population and observation period at a hospital (operators only), regional, provincial, or national level.	– CCS (2015)
	▪ Components of a QA/QI programme include:	
	– It should be dedicated to the lab but not be independent of the other hospital programmes.	– ACCF/SCAI (2012)
	– Designated clinicians from each cardiology department to lead the audit process and ensure that infrastructure is in place.	– BCIS and BCS (2015)
	– Dedicated, trained personnel to perform chart abstraction, data entry, registry query, and report generation/distribution.	– SCAI (2016)
	– Support of hospital administrators, who can help provide resources for registry participation, conduct analyses, and support other aspects of the QI process.	– ACCF/AHA/SCAI (2013)
	– A Quality Committee that:	
	▪ Includes a director, manager, and representatives of other stakeholders	▪ SCAI (2016)
	▪ Is independent and includes both physicians and relevant healthcare personnel. Interventional cardiologists are best suited to perform the primary role in evaluating PCI quality and leading the quality assurance program.	▪ ACCF/AHA/SCAI (2013)
	▪ Is responsible for reviewing metrics of quality, such as completion of time-outs, quality assurance checks of equipment, door-to-balloon times, etc.	▪ SCAI (2016)
	– Monthly multidisciplinary team meetings.	– SCAI/ACC/AHA (2014)
	▪ Functions of a QA/QI programme include:	
	– Reviewing quality and outcomes of the entire programme	– ACCF/AHA/SCAI (2013), CCN (2013), CSANZ (2014a), CSANZ (2014b)
	▪ Satisfactory outcomes should be defined by each local facility based on national or regional benchmarks.	▪ SCAI/ACC/AHA (2014)
	▪ Programmes that fail to meet their established criteria for satisfactory performance for 2 consecutive quarters must undertake efforts to improve, engaging outside experts if necessary. Failure to improve	▪ SCAI/ACC/AHA (2014)

Criteria regarding	Recommendation(s)	Organisations
	quality metrics should be grounds for programme closure regardless of the location.	
	▪ All major complications should be reviewed at least every 6 months.	▪ ACCF/SCAI (2012)
	▪ Primary PCI centres consistently performing <150 cases/year should consider whether local transfer times would support coalescing with adjacent sites.	▪ BCIS (2016)
	– Reviewing results of individual operators	
	▪ Low-volume operators (<50 PCIs annually) should undergo a more intensive review process.	▪ ACCF/AHA/SCAI (2013)
	▪ Comparison of individual and aggregate outcomes against national standards and benchmark databases.	▪ ACCF/AHA/SCAI (2013)
	▪ For all unexpected mortality and morbidity.	▪ BCIS and BCS (2015)
	▪ Complication rates exceeding national benchmarks for 2 contiguous 6-month periods should be reviewed by the QA director.	▪ ACCF/SCAI (2012)
	– Risk adjustment	– ACCF/AHA/SCAI (2013), SCAI (2016)
	▪ Requires that the institution maintain meticulous and confidential records that include patients' demographics and clinical characteristics.	▪ ACCF/AHA/SCAI (2013)
	▪ Institutions that falls >2 standard deviations outside the risk-adjusted national benchmarks in mortality or emergency same-stay CABG during 2 of 3 contiguous 6-month periods should have an external audit looking for opportunities to improve quality of care.	▪ ACCF/SCAI (2012)
	– Providing peer review auditing of individual and procedural results	– CSANZ (2014b), CSANZ (2016), SCAI (2016)
	▪ Of difficult or complicated cases	▪ ACCF/AHA/SCAI (2013)
	▪ Including assessing the appropriateness of the interventional procedures including both the clinical criteria for the procedure and the quality and interpretation of the angiograms.	▪ ACCF/AHA/SCAI (2013), CSANZ (2014a)
	▪ Regular mortality/morbidity review by the cardiologists and others as appropriate.	▪ CSANZ (2014a)
	– Performing random case reviews.	– SCAI (2016)
	– Performing formalised periodic case reviews.	– CSANZ (2014a)
	▪ Quarterly	▪ SCAI (2016)

Criteria regarding	Recommendation(s)	Organisations
	– Providing confidential and constructive feedback of performance and outcomes data to promote changes in practice and improve performance.	– ACCF/AHA/SCAI (2013)
	– Promote coordinated care between EMS, Referring Hospitals and PCI Centres	– CCN (2013)
	▪ Drive times and the rate of complications should be monitored to determine whether there is a relationship between these variables.	▪ CCN (2013)
	▪ Auditing of facilities:	
	– Is mandatory for each new interventional centre within the first 6 months of activity.	– SSC (2014)
	– Will be provided further only by necessity/on special request.	– SSC (2014)
	Quality Indicators/KPIs:	
	▪ Pre-interventional	
	– Adherence to guideline-recommended pre-treatment	– ESC/EACTS (2019), SCAI/ACC/AHA (2014)
	– The percent of direct referrals from the ambulance service.	– NHS England (2013)
	▪ Interventional technique	
	– Procedural success	– ACCF/SCAI (2012), ESC/EACTS (2019)
	– Percentage of radial arterial access	– ESC/EACTS (2019)
	– Percentage of drug-eluting stent implantation	– ESC/EACTS (2019)
	– Rate-based outcomes (outcomes related to volume)	– ACCF/SCAI (2012)
	– Cardiac catheterisation rates	– ACCF/SCAI (2012)
	– Proportion of eligible patients receiving reperfusion therapy	– CCN (2013), SCAI/ACC/AHA (2014)
	– Proportion of patients who do not undergo acute catheterisation because of misdiagnosis	– CCN (2013), SCAI/ACC/AHA (2014)
	– Percentage of STEMI patients who get primary PCI or thrombolysis reperfusion therapy or are contraindicated. Target of 80% to get primary PCI	– HSE/RCPI (2012)
	– Ratio of the number of overall PCI performed to the number of overall patients treated.	– SSC (2014)
	– Ratio of STEMI patients receiving primary PCI versus fibrinolysis.	– CCN (2013)
	– Rates of revascularization procedures (PCI and CABG) following diagnostic coronary angiography.	– SSC (2014)
	▪ Peri-interventional outcome rates	

Criteria regarding	Recommendation(s)	Organisations
	– Death	– ACCF/SCAI (2012), ESC/EACTS (2019), SCAI/ACC/AHA (2014)
	▪ Standardised in-hospital mortality, STEMI related mortality, procedure related versus non-procedure related mortality, and mortality after or during cardiopulmonary resuscitation.	▪ SSC (2014)
	– Peri-procedural myocardial infarction	– ACCF/SCAI (2012), ESC/EACTS (2019)
	– Stroke	– ACCF/SCAI (2012), ESC/EACTS (2019)
	– Contrast-induced nephropathy	– ESC/EACTS (2019)
	– Major bleeding (Bleeding Academic Research Consortium 3 - 5)	– ESC/EACTS (2019)
	– Emergency cardiovascular surgery	– ACCF/SCAI (2012), ESC/EACTS (2019)
	– Respiratory arrest	– ACCF/SCAI (2012)
	– Perforation of vessel of heart with sequelae	– ACCF/SCAI (2012)
	– Nerve injury	– ACCF/SCAI (2012)
	– Radiation injuries	– ACCF/SCAI (2012)
	▪ Discharge	
	– Antiplatelet medication prescription	– ESC/EACTS (2019)
	– High-dose lipid lowering treatment prescription	– ESC/EACTS (2019)
	– Adherence to guideline-recommended discharge medications depending on clinical setting	– ESC/EACTS (2019)
	– Percentage of eligible ACS patients who receive recommended medications and smoking cessation on discharge. Target: 90% of eligible patients	– HSE/RCPI (2012)
	– Percentage of ACS patients, admitted as an emergency, who are referred to an early Cardiac rehabilitation programme/secondary prevention programme on discharge (First appointment within 4 weeks of discharge). Target: 90% of eligible patients	– HSE/RCPI (2012)
	▪ Follow-up	
	– Readmission rates	– ESC/EACTS (2019)
	▪ Access site complications	▪ ACCF/SCAI (2012)
	▪ Access site complications requiring surgery	▪ ACCF/SCAI (2012)

Criteria regarding	Recommendation(s)	Organisations
	– 30 day and 1 year mortality	– ESC/EACTS (2019)
	– Unplanned repeat revascularisation at 1 year	– ESC/EACTS (2019)
	– Stent thrombosis according to Academic Research Consortium criteria	– ESC/EACTS (2019)
	– Major bleeding (Bleeding Academic Research Consortium 3 - 5)	– ESC/EACTS (2019)
	– Composite of all-cause death, any myocardial infarction, and any unplanned repeat revascularisation at 1 year	– ESC/EACTS (2019)
	▪ Individual physician MACCE	▪ ACCF/SCAI (2012)
	– Proportion of patients who undergo acute catheterisation and are found to have no elevation in cardiac biomarkers and no revascularisation in the first 24h	– SCAI/ACC/AHA (2014)
	– Proportion of fibrinolysis STEMI patients who are catheterised within 24 hours of fibrinolysis	– CCN (2013)
	▪ Timing outcomes	
	– Door-to-balloon times	– ACCF/SCAI (2012)
	▪ For walk-in patients arriving at PCI Centre: Target: 90 minutes	▪ CCN (2013)
	▪ For patients arriving at Referring Hospital: Target: 120 minutes	▪ CCN (2013)
	▪ STEMI Referral Hospital ED door-to-balloon (first device used) time	▪ SCAI/ACC/AHA (2014)
	▪ Target: 90% to be ≤90 minutes	▪ HSE/RCPI (2012)
	▪ Target: <45 minutes for daytime presenters and for those patients about whom there has been advance warning (direct ambulance referrals and inter-hospital transfers).	▪ NHS England (2013)
	▪ Target: ≥75% to be <60 minutes (excluding cardiogenic shock and out-of-hospital arrest).	▪ BCIS (2016)
	– Door-to-first device time, non-transfer patients	– SCAI/ACC/AHA (2014)
	– First medical contact to balloon inflation (first device used) time.	
	▪ Target for EMS with field ECG to cath lab: 90 minutes	▪ CCN (2013)
	▪ For non-transfer and transfer patients	▪ SCAI/ACC/AHA (2014)
	▪ Target: 90% to be ≤120 minutes.	▪ HSE/RCPI (2012)
	– Call-to-balloon time	
	▪ Target: >75% to be <150 minutes	▪ NHS England (2013)
	– Door-to-needle time	
	▪ Target: 90% to be ≤30 minutes	▪ HSE/RCPI (2012)

Criteria regarding	Recommendation(s)	Organisations
	▪ For in-hospital lysis: Target ED arrival to administration of lytic: 30 minutes	▪ CCN (2013)
	▪ For pre-hospital lysis: Target scene arrival to administration of lytic: 30 minutes	▪ CCN (2013)
	– Time to first ECG	
	▪ Target: 10 mins	▪ CCN (2013)
	– Time from arrival at ED to departure from ED (EMS transfer)	
	▪ Target: 30 mins	▪ CCN (2013)
	– Length of stay in hospital	
	▪ Target: median of 4 days for STEMI and 5 days for NSTEMI	▪ HSE/RCPI (2012)
	▪ Service outcomes	
	– Access to facility information	– ACCF/SCAI (2012)
	– Satisfaction surveys	– ACCF/SCAI (2012)
	▪ Financial outcomes	
	– Procedural costs (as laboratory and as individual physician)	– ACCF/SCAI (2012)
	– Risk management/litigation costs	– ACCF/SCAI (2012)

Key: ACC(F) – American College of Cardiology (Foundation); ACS – acute coronary syndrome; AHA – American Heart Association; AMA – American Medical Association; API – Association of Physicians of India; BCIS – British Cardiovascular Intervention society; BCS – British Cardiovascular Society; CABG – coronary artery bypass graft; CCN – Cardiac Care Network of Ontario; CCS – Canadian Cardiovascular Society; CPAP – continuous positive airway pressure; CQI – continuous quality improvement; CSANZ – Cardiac Society of Australia and New Zealand; CTO – chronic total occlusion; DGK – German Cardiac Society; EACTS – European Association for Cardio-Thoracic Surgery; ED – emergency department; EMS – emergency medical services; ECG – electrocardiogram; ESC – European Society of Cardiology; GISE – Italian Group of Hemodynamic Studies; IABP – intra-aortic balloon pump; IVUS – Intravascular ultrasound; JCS – Japanese circulation Society; KPI – key performance indicator; MACCE – major adverse cardiovascular and cerebrovascular events; NVVC – Netherlands Association of Cardiology; PCI – percutaneous coronary intervention; PTCA – Percutaneous transluminal coronary angioplasty; PTCRA – Percutaneous transluminal rotational atherectomy; PTK – Polish Cardiac Society; QA – quality assurance; QI – quality improvement; RCPI – Royal College of Physicians in Ireland; SCAI – the Society for Cardiovascular Angiography and Interventions; SICI – Italian Society of Invasive Cardiology; SSC – Swiss Society of Cardiology; STEMI – ST-elevation myocardial infarction.

† High-risk PCIs include: (Combined list. For specific lists see Table A.16 in Appendix 4)
Patients with:
– Left ventricular ejection fraction ≤30% / <25%
– Unprotected left main stenosis

- Single or multiple target lesions that in aggregate jeopardise over 50% of the remaining viable myocardium
- Decompensated congestive heart failure (Killip Class 3 to 4)
- Recent (<8 weeks) cerebrovascular accident
- Known clotting disorder
- Chronic kidney disease (creatinine >2.0 mg/dL or creatinine clearance<60 mL/min)
- Serious ongoing ventricular arrhythmias.

Target lesion with:
- Excessive proximal tortuosity or lesion angulation
- Moderate or greater calcification of the target lesion or proximal segment
- Bifurcation lesions (side branch > 2.25mm) where iatrogenic occlusion of a side branch would be an indication for emergency CABG
- Degenerative vein grafts
- Chronic total occlusion
- Left main stenosis ≥50% or 3-vessel disease (>70% proximal or mid lesions) unprotected by prior bypass surgery
- Target lesion that jeopardizes an extensive amount of myocardium. Jeopardy scoring systems, such as SYNTAX, may be useful in defining the extent
- Diffuse disease (>20 mm length)
- Thrombus in vessel or at lesion site
- Vessel characteristics that, in the operator's judgment, would impede stent deployment
- Anticipated probable need for rotational or other atherectomy device, cutting balloon, or laser.

3.3.4 Methodological quality of included studies

To evaluate the quality of the guidance documents included in the review, the AGREE II instrument was used.[213-215] It comprises 23 items organised into six domains, with each item being rated on a seven-point Likert scale from one ('strongly disagree') to seven ('strongly agree'). The domain scores for each of the guidance documents are shown in Table 3.5 and Figure 3.2. In Figure 3.2, the top and bottom of the box plot are the 75th and 25th centiles, respectively, the middle line is the median, the diamond is the mean while the error bars represent the range of scores.

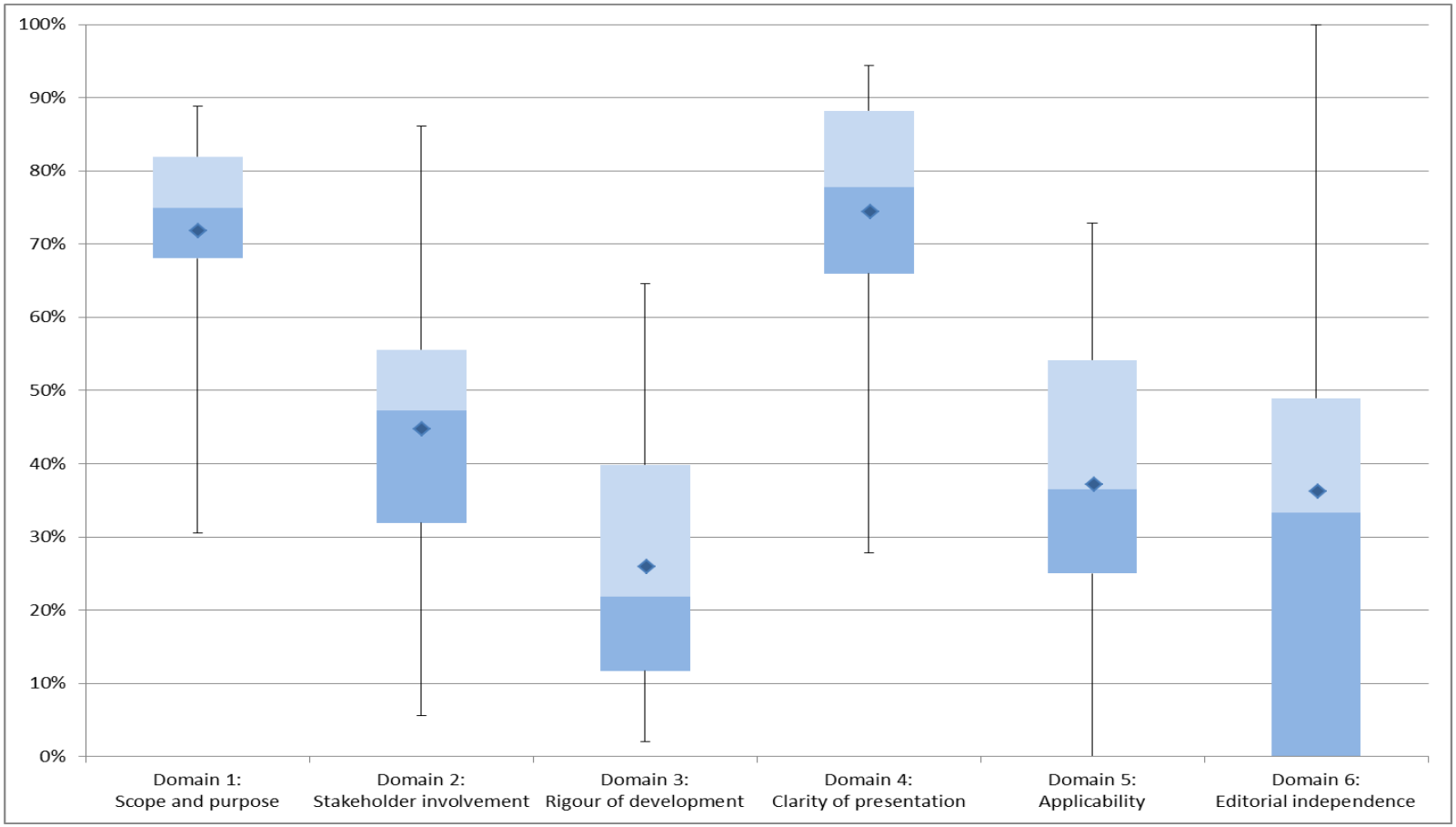
Table 3.5 Quality appraisal of guidance documents presented as scaled domain scores using AGREE-II instrument

Domain	Scope and purpose (%)	Stakeholder involvement (%)	Rigour of development (%)	Clarity of presentation (%)	Applicability (%)	Editorial independence (%)
Asia						
CSANZ (2014a)	33	31	9	86	21	0
CSANZ (2014b)	75	31	11	83	25	33
CSANZ (2016)	31	28	24	75	23	38
API (2011)	72	36	13	47	0	0
JCS (2013)	78	39	41	75	19	0
Europe						
ESC/EACTS (2019)	83	67	56	94	42	100
DGK (2015)	56	53	10	78	27	33
HSE/RCPI (2012)	83	47	4	94	29	0
SICI-GISE (2015)	72	47	13	56	54	46
NVVC (2016)	64	39	23	89	25	0
PTK (2013)	78	61	2	64	0	42
SSC (2014)	72	19	15	89	38	0
NHS England (2013)	86	6	32	75	35	0
BCIS and BCS (2015)	72	28	19	94	54	50
BCIS (2016)	83	47	4	94	29	0
North America						
CCN (2013)	78	58	38	78	60	0
CCS (2015)	67	42	21	86	65	79
ACCF/SCAI (2012)	89	61	44	39	38	100
ACCF/AHA/SCAI (2013)	78	56	65	86	63	100
SCAI/ACC/AHA (2014)	67	47	51	72	73	46
ACC/AHA/SCAI/AMA (2014)	86	86	54	28	42	96
SCAI (2016)	75	56	23	50	56	33

Key: ACC(F) – American College of Cardiology (Foundation); AHA – American Heart Association; AMA – American Medical Association; API – Association of Physicians of India; BCIS – British Cardiovascular Intervention society; BCS – British Cardiovascular Society; CCN –Cardiac Care Network of Ontario; CCS – Canadian Cardiovascular Society; CSANZ – Cardiac Society of Australia and New Zealand; DGK – German Cardiac Society; EACTS – European Association for Cardio-Thoracic Surgery; ESC – European Society of Cardiology; GISE – Italian Group of Hemodynamic Studies; JCS – Japanese circulation Society; NVVC – Netherlands Association of Cardiology; PTK – Polish Cardiac Society; RCPI – Royal College of Physicians in Ireland; SCAI – the Society for Cardiovascular Angiography and Interventions; SICI – Italian Society of Invasive Cardiology; SSC – Swiss

Society of Cardiology.

Figure 3.2 Quality appraisal of guidance documents presented as the scaled domain score using the AGREE-II instrument



Key: Top and bottom of the box plot are the 75th and 25th centiles, respectively, the middle line is the median score, the diamond is the mean score while the error bars represent the range of scores.

Domain 4 (clarity of presentation) had the highest average score of all the domains (mean 74%, median 78%), but a wide range of scores (28-94%). For most guidance documents the recommendations were specific and unambiguous and the key recommendations were easily identifiable. The lowest scoring in this domain was an ACC/AHA/SCAI/AMA guidance document from 2014 on performance measures for adults undergoing PCI: the recommendations given were ambiguous, no other options for management of the health condition were given, and key recommendations were difficult to find.[267]

For Domain 1 (scope and purpose) the guidance documents generally scored well (mean 72%, range 31-89%) Two documents from the CSANZ,[251, 253] a position statement and a guideline, scored poorly in this domain as no clear objectives or health questions were stated.

Domain 2 (stakeholder involvement) had a mean score of 45% with a minimum score of 6% and a maximum score of 86%. However, a detailed overview of stakeholder involvement and the views and preferences of the target population may not be necessary for non-guideline documents. When only including those guidance documents that identified themselves as guidelines (n=6),[12, 253-256, 259] the mean score for Domain 2 was 47% (range 28-67%), suggesting this domain was poorly reported across the different types of guidance documents. The lowest-scoring documents in this domain were a standard contract document from NHS England 2013[261] and a position statement from the Swiss Society of Cardiology 2014.[260] Neither made any mention of the development group, the views of the target population or a definition of the target users for the guideline. However, the position paper did provide a list of authors.

Domain 5 (applicability) had a mean score of 37% (range 0-73%); two guidance documents scored zero for this domain[254, 259] as they had no mention of facilitators or barriers to the application of the guidance, no consideration of resource implication and no mention of monitoring and auditing criteria. The highest-scoring documents for this domain were guidance documents from North America[11, 178, 265] which scored between 63% and 73% for applicability. Very few guidance documents considered the potential costs of applying the recommendations.[175-178, 255, 257, 268]

Domain 6 (editorial independence) was the most variable in terms of scoring. Nine out of 22 guidance documents scored zero in this domain[175-177, 251, 254, 255, 258, 260, 261, 263, 264] as they had no conflicts of interest statement and no mention of the funding body, while three other documents scored 100% in this domain.[11, 12, 266]

Overall, the lowest-scoring domain was Domain 3 (rigour of development) (mean 26%, median 22%, range 2-65%). This domain was poorly reported in most of the

guidance documents. The highest-scoring document in this domain was a clinical competence statement from the ACCF/AHA/SCAI in 2013.[11] It included a systematic search of the literature, the strengths and limitations of the body of evidence, an explicit link between recommendations and supporting evidence and the guideline was externally reviewed prior to publication. Many of the other guidance documents provided no evidence of systematic methods to find evidence and no clear link between the evidence and the recommendations. However, it is debatable whether this domain should be fully applied to the non-guideline documents. Position statements are often a short one- to two-page document that lay out the key recommendations from a society or organisation on a particular topic. Given the concise nature of these documents, a thorough review of the evidence may not be expected to be provided. These documents may have an evidence base and a rigorous method of development behind them, but this is not clearly stated. The six guidelines that were included[12, 253-256, 259] scored between 2% and 56% for this domain, suggesting the rigour of development was poor or poorly described across the different types of guidance documents and not just in position statements. Only three of the guidance documents made any mention of updating the guideline.[12, 260, 266]

Overall, the quality of the guidance documents was good for Domain 1 (scope and purpose) and Domain 4 (clarity of presentation), moderate for Domain 2 (stakeholder involvement), poor for Domain 5 (applicability), highly variable for Domain 6 (editorial independence) and very poor for Domain 3 (rigour of development). Two guidance documents scored consistently well across all domains: a clinical competence statement from the ACCF/AHA/SCAI in 2013 and the ESC/EACTS 2019 guidelines.

3.4 Discussion

This systematic review collated international guidance documents pertaining to service provision for PCI centres, synthesised the organisational and service criteria from these documents, and appraised the document quality. For each of the outcomes included there were common themes that a number of guidance documents agreed on and additional recommendations that only one or two guidance documents provided. For the majority of guidance documents, the evidence base for the recommendation was unclear. Of the four guidance documents that stated a review of the literature was undertaken,[11, 12, 178, 264] only one included a date range.[178] It is therefore not possible to assess whether the guidance documents are based on the most up-to-date evidence. A recent article that specifically looked at ACC/AHA and ESC guidelines from 2008-2018 to evaluate the levels of evidence used in making recommendations, found that only a small proportion of recommendations (8.5-14.2%) were supported by high levels of

evidence.[270]

In terms of institutional facilities, there was considerable variation in the level of detail reported across guidelines. Most agreed upon the basic facilities necessary for a PCI centre, such as physiological assessment, imaging, radiation protection and monitoring equipment, cardiac lab equipment, a ventilator and full resuscitation facilities. In addition, a number of guidance documents specifically recommended that, for centres that provide primary PCI services, there should be at least two cath labs,[175, 258, 261, 263, 264] an ICU[175, 257, 259-261] and that the service should be available 24 hours a day, seven days a week.[12, 175, 178, 257-261, 263, 264, 266] However, these recommendations were not consistent across all guidance documents.

There was considerable variation in the recommendations regarding the minimum number of procedures an institution or operator should perform per year in order to maintain optimal performance. The US recommendations for PCI and primary PCI at an institutional or operator level were generally lower than those recommended in countries such as the UK and the Netherlands. This may be to do with the current configuration of specialist cardiac services in these countries and the geographical distribution of the population rather than the evidence base underpinning these recommendations. It was discussed in the guidance documents that the relative benefits of higher-volume facilities needs to be weighed against the potential decline in timely access in less populated areas when care is regionalised, particularly for patients requiring emergency PCI.[11]

One of the guidance documents from the ACC/AHA/SCAI/AMA 2014 recommended that no specific threshold be set as it was concerned that an unintended consequence of providing thresholds may be that operators who have not reached the threshold may perform unnecessary PCI procedures. They also recommended that future guidelines should address whether adjunctive coronary procedures such as intravascular ultrasound and non-coronary procedures such as transcatheter aortic valve implantation (TAVI) could be included in measures of operator and institutional volume given that the techniques require overlapping technical skills. The BCIS in 2015 made recommendations regarding operator volume that included a proportion of interventional diagnostic procedures (Table 3.4 and

Table A.15).[262] Previously published systematic reviews on the volume outcome relationship for PCI have reported contrasting results,[8, 9, 271] and no optimal threshold value has been reported. The relationship is systematically reviewed in Chapter 4.

There was general agreement from the guidance documents that centres without on-site surgical backup can perform PCI as long as procedures and protocols are in place to transfer patients to a surgical facility within a specified time period and that complex cases should not be performed at these centres.

As might be expected, recommendations about staffing levels and the type of staff to resource a PCI centre differ greatly depending on the size of the PCI facility and the country. Consistent with other recommendations, the evidence base underpinning the staffing levels was poorly documented. Between two and four interventional cardiologists were recommended per PCI centre, but the number and type of support staff per interventional cardiologist differed between the guidance documents. A number made recommendations as to how many interventional cardiologists are required to provide a 24 hours a day, seven days a week service, with consideration given to operator volume recommendations and minimum break periods for staff; however, this was not consistently reported. It is possible that the staff levels are informed by working time directives and usual staff contractual arrangements. Furthermore, staffing rosters may be organised to minimise the time spent by individual staff members in cardiac catheterisation laboratories given the significant occupational health risks associated with long-term ionising radiation exposure.[272]

Time-to-treatment was mentioned in 15 of the 22 guidance documents included in this review, as well as 30 additional guidance documents (listed in Appendix 5). There were a number of common themes around acceptable timing until the patient receives treatment and transport times. The terminology and the exact section of the patient pathway examined differed between guidelines. Door-to-balloon time was most often reported, with the majority of studies recommending a time of less than 90 minutes, but others reported the time from first medical contact-to-balloon time or door-to-needle time, making direct comparisons difficult. There were particular requirements around the establishment of new centres and centres without on-site surgical backup.

Monitoring of standards and KPIs was an outcome covered by most of the guidance documents. The guidance documents agreed that a database was necessary in order to monitor KPIs at an operator, hospital, regional, and national level. The ability to benchmark institutes and operators based on this data was also an important factor with some sort of feedback mechanism to address/review outcomes and problems. A number of KPIs were proposed by the guidance documents around interventional

techniques, post-procedural outcome rates, discharge medication and time to treatment. These can be useful especially when a service is first established, to ensure that it is at the same standard as other, similar centres or to identify reasons for differences across centres. A number of guidelines noted that KPIs such as procedural volume are not standalone measures of quality of care but should be considered as one of several factors when assessing the quality of an operator or institution.[11]

The strength of this review is the use of a systematic methodology to identify and extract data regarding PCI services. In terms of limitations, the review found a lack of clarity around the evidence base used to make the recommendations and therefore there is very low certainty around the recommendations presented in this review.

3.5 Conclusions

PCI is a complex intervention which is rapidly evolving over time. Recommendations regarding PCI centres and services vary between countries, societies and the type of PCI being carried out. It was often unclear what the evidence base was behind these recommendations; however, there were common themes and agreement between the guidance documents.

3.6 Key points

- Twenty-two guidance documents were included in the review. Ten from Europe, seven from North America and five from the Asia-Pacific region.
- The guidance documents were quality appraised and overall they scored well in terms of stating the scope and purpose of the document and clearly presenting the recommendations, but scored poorly in the rigour of development domain (often it was unclear what evidence underpinned the recommendation) and most made no conflict of interest or funding statement.
- Guidance documents made recommendations on institutional facilities (n=16), institutional volume (n=19), operator volume (n=17), surgical cover (n=11), staffing levels (n=12), time/distance to treatment (n=15), and monitoring of standards (n=19).
- The minimum recommended number of primary and total PCI procedures per centre ranged from 36 to 150 and from 200 to 600 procedures per year, respectively.
- The minimum recommended number of primary and total PCI procedures performed by an operator ranged from 11 to 30 and from 50 to 150 procedures per year, respectively.
- Institutional and operator volume: the recommended minimum procedural volume was lower in US guidance documents compared with the UK and the Netherlands.
- Elective and primary PCI may be considered in hospitals without on-site cardiac surgery provided that there are clear and documented systems in place for the urgent transfer of patients to a facility with cardiovascular surgical support which can occur within recommended timeframes.
- In general there was a lack of agreement on staffing levels. At least one interventional cardiologist and one to four additional staff were recommended per PCI procedure. Between two and four interventional cardiologists were recommended per primary PCI centre, depending on the number of rooms and if the service was provided 24/7.
- Time-to-treatment metrics were inconsistently reported. The most often reported was a door-to-balloon time of <90 minutes for STEMI patients. Other KPIs included 'first medical contact'-to-balloon time <120 minutes and call-to-balloon time <150 minutes. Use of thrombolysis as an alternative to primary

PCI was recommended if transport time exceeded 90 minutes (n=2) or 120 minutes (n=3).

- There was general agreement between the guidelines in recommending the creation of local databases to allow for the recording and monitoring of procedures and outcomes and national or regional registries to allow benchmarking and tracking of complications. A number of different KPIs were recommended by the guidelines, most commonly in regard to time-to-treatment, interventional technique and interventional outcomes.

4 Review question three: PCI volume-outcome relationship

4.1 Introduction

The volume-outcome relationship refers to the association between higher volumes of procedures and better patient outcomes. This phenomenon has been observed for many complex surgical procedures.[7, 273] The hypothesis underpinning this volume-outcome relationship is that 'practice makes perfect', that is, hospitals or operators that perform a larger number of procedures will achieve better outcomes than those that perform relatively fewer procedures.[274]

There have been at least three previous systematic reviews examining the volume-outcome relationship.[8-10] Two of these have found that there was a significant inverse relationship between hospital PCI volume and postoperative mortality.[8, 9] Evidence from these studies has informed guidelines and policy, and led to minimum volume criteria being recommended (for example, ≥200 hospital PCI procedures per year by the ACCF/AHA/SCAI guideline group).[11] These criteria in turn have informed healthcare policy standards (for example, restricting reimbursement to procedures undertaken in facilities meeting minimum volume criteria) and service provision standards (for example, minimum requirements for referrals) in certain countries.[275-277] However, the third systematic review examining the relationship between operator PCI volume and postoperative mortality did not find a significant association.[10] Furthermore, many commentators in this area have argued that due to advances in PCI techniques and postoperative medical management and regionalisation of care in recent times, the volume-outcome relationship has become attenuated over time, and should no longer been prioritised as a key metric for PCI service delivery.[13, 269, 275, 278] The aim of this systematic review and meta-analysis was therefore to examine the relationship between PCI procedural volume and patient outcomes, in light of advances in interventional cardiology.

4.2 Methods

4.2.1 Review question

What is the relationship between procedure volume and patient outcomes for PCI?

The population, intervention, comparator, outcomes and study design of interest in this review question are described in Table 4.1.

Table 4.1: PICOS for RQ3

Population	Adults (18 years or older) requiring PCI (primary or elective) for cardiac conditions

Intervention	Highest volume hospital Highest volume operator (at an individual level)
Comparator	Lowest volume hospital Lowest volume operator (at an individual level)
Outcomes	**Primary:** Mortality Survival (to at least three months post procedure) **Secondary:** Complications of PCI Process outcomes Healthcare utilisation outcomes
Study design	Observational

4.2.2 Search strategy

Electronic searches were conducted in PubMed, Embase, CINAHL Plus and the Cochrane Library (which includes the Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) database and the National Health Service Economic Evaluation Database (NHS EED)) for the period 1 January 2008 to 21 December 2018. The searches were updated on 28 May 2019. Due to significant advances in PCI practices and perioperative management, it was decided that only studies published since 2008 would be included.[8, 57] However, there was no limit placed on when the studies were conducted, as subgroup analysis was to be conducted specifically on studies with data from prior to 2006 compared with those using data from 2006 and onwards.

Grey literature sources were also searched (Appendix 2, Table A.5 and Table A.6), along with the first five pages of Google and Google Scholar.

The search strategy used search terms (Appendix 1) adapted from an earlier systematic review.[8] Additional search methods used included forward citation searching of eligible studies, hand searching relevant journals (*Heart*, *European Heart Journal*, *Journal of the American College of Cardiology*, *Canadian Journal of Cardiology*, *Catheterization and Cardiovascular Interventions*) and systematic reviews and searching reference lists of included studies.

4.2.3 Selection criteria

Initial duplicates were removed by one reviewer. Remaining records were independently screened by two reviewers, first by title and abstract and subsequently by full-text. Any disagreements were resolved through discussion, and, where necessary, a third reviewer. All records that were excluded after full-text

screening were reported along with their reason for exclusion.

Studies that examined the quantitative relationship between hospital or operator volume of PCI procedures and mortality or survival outcomes in adults were included according to the inclusion and exclusion criteria outlined in Table 4.2

Table 4.2: Inclusion and exclusion criteria for RQ3

Inclusion Criteria	Exclusion Criteria
▪ Subject of the study is PCI ▪ Relationship between hospital or operator volume and PCI outcomes is investigated ▪ Study uses primary data (i.e. editorials and reviews are excluded) ▪ Study reports at least one of the predefined primary outcomes of interest ▪ Study reports odds ratios (ORs), hazard ratios (HRs), relative risks (RRs), or adjusted rates (that is, outcomes must have been adjusted) ▪ For hospital volume studies only: does not describe the results obtained at a single centre ▪ For operator studies only: does not describe the results of a single operator	▪ Multiple publications based on the same database; only the most recent or most informative article was included ▪ No definition of procedural volume as a distinct number (for example a continuous variable) or cut-off values (studies that defined volume as "specialisation" were excluded) ▪ No postoperative outcomes reported (that is, mortality or survival) ▪ Conference papers and abstracts where the full paper was unobtainable ▪ Paper published prior to 2008 ▪ Paediatric (<18 years old) population

4.2.4 Data extraction and management

The results of the search were exported to Covidence (www.covidence.org) which was used to manage citations and perform title and abstract screening. Duplicates were identified and removed. A flow diagram using PRISMA guidelines was generated to report the selection process and all results (Figure 4.1). Data were extracted for all included studies. Study authors were contacted for additional information, if required. Data extraction was performed independently by a minimum of two people with any disagreements being resolved by discussion, and, where necessary, a third reviewer. The data extraction tool was piloted on two studies initially. For this review question Covidence was also used for data extraction and management purposes.

The following data were extracted from each included study:

- year of publication
- country
- database
- data type (for example administrative or clinical)
- study period
- study design (as classified by study authors)
- number of patients/procedures
- number of hospitals
- number of operators
- hospital volume classification (in terms of cases per year)
- definition of high-volume hospital
- definition of high-volume operator
- how cut-points are selected (for example data-driven, guideline-based)
- volume grouping (for example quartiles, median)
- risk adjustment covariates
  - process measures (for example distance to hospital, time to treatment, out of hospital cardiac arrest, radial artery access, use of drug-eluting stents)
  - demographics of patient population (for example sex, indication, stent)
  - patient comorbidities (for example heart failure)
  - hospital cluster effect
  - hospital characteristics (for example presence of on-site surgical cover)
  - severity of disease (for example cardiogenic shock)
  - treatment differences (for example salvage PCI)
- difference in findings between middle groups and highest/lowest groups.

The primary outcomes:

- mortality
- survival (minimum follow-up period of three months).

The secondary outcomes:

- complications of PCI (for example major adverse cardiac events (MACE)/ major adverse cardiac and cardiovascular events (MACCE), emergency coronary artery bypass graft (CABG), bleeding, peri-procedural myocardial infarction, vascular complications, stroke, contrast-induced nephropathy and stent thrombosis)
- process outcomes (for example time-to-treatment and appropriateness of PCI)
- healthcare utilisation outcomes (for example hospital readmission, hospital length of stay, unplanned repeat vascularisations).

4.2.5 Quality appraisal

Quality appraisal of the included studies was conducted independently by two reviewers based on a modified version of the Critical Appraisal Skills Programme (CASP) tool for

cohort studies.[279] The tool was piloted by two reviewers initially. Any disagreements were resolved by consensus, or arbitration by a third reviewer if necessary.

4.2.6 Data synthesis

The guidelines for evaluating the clinical effectiveness of health technologies in Ireland were adhered to with regard to data synthesis.[280] The following points summarise the synthesis approach adopted. This approach was in line with an earlier study's methods:[8]

- Meta-analysis was performed for our primary outcome, if appropriate, to determine the relationship between:
  - hospital volume and postoperative mortality
  - operator volume and postoperative mortality.
- Meta-analyses were conducted separately for studies reporting outcomes for total PCI procedures and for studies reporting outcomes for primary PCI procedures only. Primary PCI is defined as urgent balloon angioplasty, without the previous administration of platelet glycoprotein IIb/IIIa inhibitors or thrombolytic therapy, to open the infarct-related artery during a STEMI.[281]
- To avoid the issue of double counting in the meta-analyses and hence potentially overstating the evidence, a maximum of one study from each data source was included in each meta-analysis, with the most comprehensive or recent data source chosen.
- Pooled estimated effect sizes were calculated using the adjusted outcomes of the highest volume or operator group compared with the lowest volume group (reference). If the highest volume group was used as the reference, the results were transformed (1/effect size) to fit the statistical model.
- Where several models were used for adjustment, the choice of model to use in the meta-analysis was based on goodness-to-fit (where reported by the primary authors). Otherwise the plausibility of the covariates was used (taking into account the choice of covariates used by the primary authors). Where studies reported analyses based on multiple plausible thresholds, the model using a threshold most similar to other included studies was selected.
- In studies that presented findings in graph form only (groupings presented as risk ratios relative to the overall mean), mean and 95% confidence interval (CI) for the upper and lower quantiles were extracted from the graphs using the online resource WebPlotDigitizer (automeris.io/WebPlotDigitizer). Based on the reported distributions relative to the overall mean, Monte Carlo simulation was

used to determine the distribution of the relative risk of mortality between the lower and upper quantiles. Using baseline mortality rates, the estimated risk ratios were converted to odds ratios for inclusion in the meta-analyses.

- RevMan version 5.3 was used to conduct the random-effects, inverse-variance meta-analysis.

- In-hospital or 30-day mortality were considered the primary outcomes in the meta-analysis. Where a study reported mortality at both time points, the 30-day outcome was used, due to the fact that risk of death after PCI is highest during the first two weeks after the procedure (which often extends beyond the index hospitalisation).[282]

- The Cochrane Handbook version 5.1 was used to define heterogeneity.[283] According to the Cochrane handbook; an I^2 score of 0% to 40% might not be important; an I^2 score of 30% to 60% may represent moderate heterogeneity; an I^2 score of 50% to 90% may represent substantial heterogeneity; and an I^2 score of 75% to 100% may represent considerable heterogeneity.

- Sensitivity and subgroup analyses were also conducted to explore possible explanations for heterogeneity and to assess the effect of various subgroups on the overall outcome. Planned subgroup analyses conducted included study quality, different continental regions, unadjusted vs. adjusted odds, degree of completeness of case-mix adjustment (considered complete if adjusted for age, sex, severity of disease and comorbidity), different definitions for low-volume hospital (<400 PCI procedures per year vs. ≥400 PCI procedures per year,[262] or <36 primary PCI procedures per year vs. ≥36 primary PCI procedures per year),[11] different definitions for low-volume operators (<75 PCI procedures per year vs. ≥75 PCI procedures per year,[262] or <50 primary PCI procedures per year vs. ≥50 primary PCI procedures per year)[262], study data period (pre 2006 vs. 2006 onwards) and selected high-risk subgroups (i.e. emergent [PCI should be performed as soon as possible][284]/urgent cases [PCI should be performed on an inpatient basis and before discharge],[284] multi-vessel PCI, cardiogenic shock, LMPCI, CTO and myocardial infarction (MI)). A post-hoc subgroup analysis was also conducted to examine the difference in the pooled effect estimate between studies reporting in-hospital mortality and 30-day mortality.

- Although the main focus of analysis was the highest and lowest groupings, the risk-adjusted findings from middle groups were also noted to observe for trends in differences.

- A random-effects meta-regression analysis was also performed to explore the potential causes of heterogeneity between studies. As we had fewer than ten

studies in each meta-analysis, this analysis was exploratory in nature. Specific covariates tested included high and low cut-off values for hospital and operator volumes, continental regions, number of groupings, mean volume of lowest and highest groupings and the study period. STATA version 13 (StataCorp, College Station, TX, USA) was used to conduct the meta-regression.

- For one meta-analysis where a temporal trend was observed, a random-effects cumulative meta-analysis was conducted using STATA version 13 (StataCorp, College Station, TX, USA) using the median year of study data as opposed to the publication year. This was conducted to better track the accumulation of evidence over time.[285]
- A narrative synthesis was undertaken for the findings not included in the meta-analysis.
- Publication bias was not formally assessed as the minimum requirement of 10 studies was not met in any single meta-analysis in order to conduct this test; however funnels plots were visually inspected.
- Endnote X7.4 was used for managing references in the final report.

4.2.7 Assessing the certainty of the body of evidence using the GRADE approach

Where appropriate, summary of findings (SOF) tables using the GRADEpro software were generated for the primary outcomes of this review question.[286] The certainty of the evidence for each outcome was assessed independently by two reviewers using the GRADE approach.[287] Evidence was graded as high, moderate, low or very low quality, the definitions of which are outlined in Table 4.3 below.[287] Randomised controlled trial evidence is considered to be high quality by default, whereas observational study evidence is considered to be low quality by default. The evidence was downgraded by one level for serious (or by two levels for very serious) limitations depending on assessments of the risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias. Conversely, for observational studies only, the evidence was upgraded, depending on the assessments of magnitude of effect size, dose-response gradient and effect of plausible residual confounding.[287]

Table 4.3: Definitions of the quality rating of evidence grades

Quality rating	*Definition*
High	*'We are very confident that the true effect lies close to the estimate of the effect.'*
Moderate	*'We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.'*
Low	*'Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.'*
Very low	*'We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.'*

4.2.8 Protocol deviations

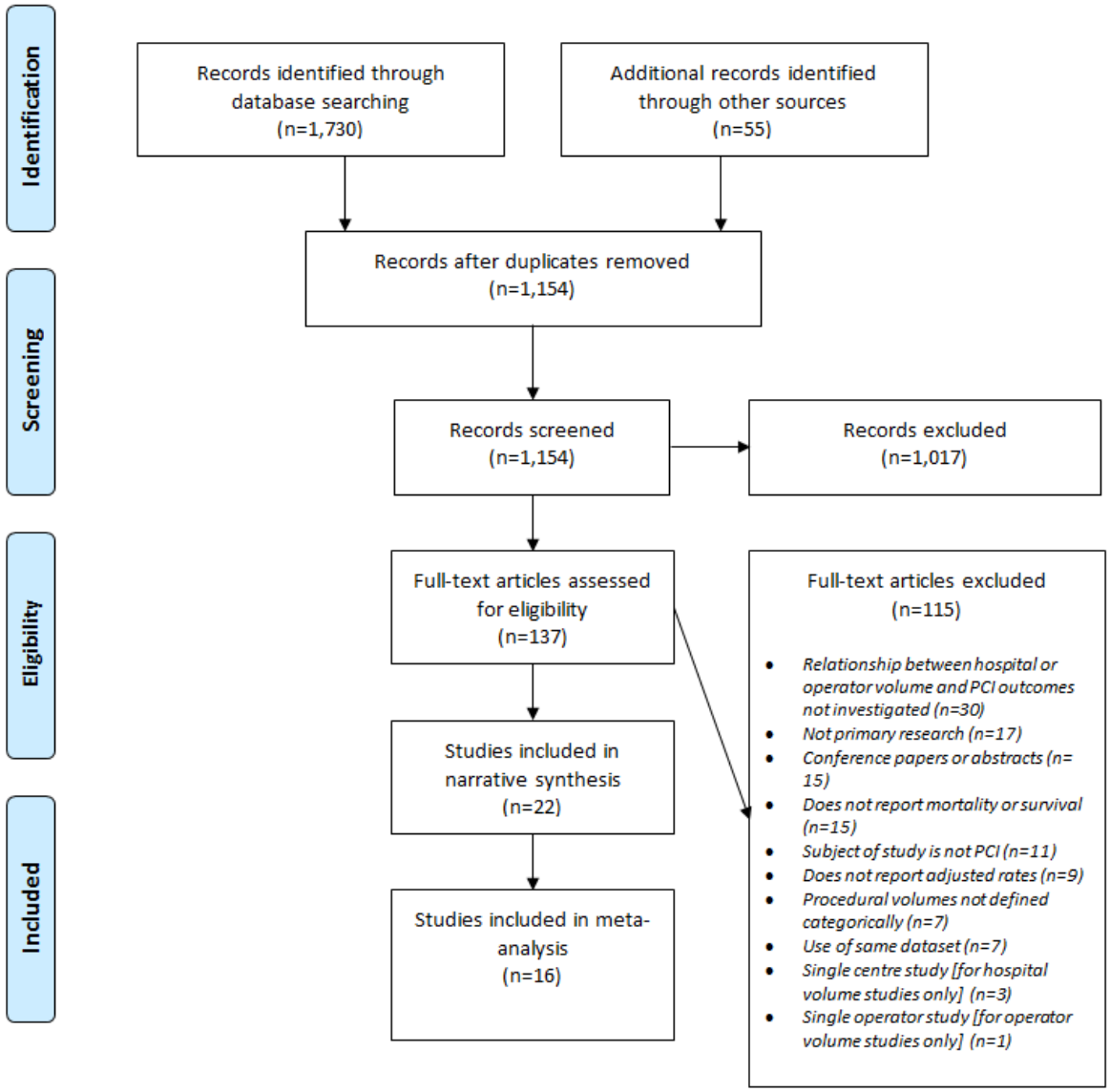
Protocol deviations are listed in Appendix 10.

4.3 Results

4.3.1 Search results

The search of listed electronic databases identified 1,730 potentially relevant records; 55 potential records were identified through searches of the grey literature and other sources. After the exclusion of duplicates, 1,154 records were screened independently by two reviewers, with a further 1,017 references excluded based on titles and abstracts. A total of 137 full-text articles were assessed for eligibility. Of these, 115 references were excluded (Appendix 6, Table A.24) according to the inclusion and exclusion criteria (Table 4.2). This resulted in 22 studies being included in the review (Figure 4.1).

Figure 4.1: PRISMA flow chart of included studies for RQ3



4.3.2 Characteristics of included studies

A summary of study characteristics is provided below in Table 4.4 with more in-depth detail provided in Appendix 3 (Table A.10).

4.3.2.1 Study country

Of the 22 included studies, ten were conducted in the US,[288-297] with the remainder conducted in Japan (n=5),[298-302] the UK (specifically England and Wales) (n=2),[271, 303] South Korea (n=1),[304] Italy (n=1),[305] China (n=1),[306] Taiwan (n=1)[307] and Germany (n=1).[308] No studies were conducted in Ireland.

Table 4.4: Table of characteristics of included studies for RQ3

First author, country (year)	Study period	Study design	Total population (patients or procedures)	Age	Male (%)	Risk adjustment	No. of groupings	Low volume definition (PCI procedures/ year)	High volume definition (PCI procedures/ year)	Mortality outcome
Adogwa, US (2009)[288]	2000-2005	Cross-sectional	75,869	55-64 years old: 48.7%, ≥65 years old: 22.2%	62.6	Age, Sex, Severity, Comorbidity	3	H: <250	H: ≥500	In-hospital
Arora, US (2016)[289]	2006-2011	Cross-sectional	107,849	65-79 years olds: 23.9% ≥80 years old: 11.7%	67.9	Age, Sex, Severity, Comorbidity, Hospital characteristics, Clustering, Treatment differences	4	H: <353	H: ≥1167	In-hospital
Badheka, US (2014)[290]	2005-2009	Cross-sectional	457,498	Mean ± SD: 64.5 ± 0.01	66.21	Age, Sex, Severity, Comorbidity, Hospital characteristics, Clustering, Treatment differences	4	H: ≤542 O: ≤15	H: >1641 O: >100	In-hospital
Barnett, US (2018)[291]	2008-2011	Retro-spective cohort study	13,237	Mean ± SD: 59.3 ± 5.1	97.9	Age, Sex, Severity, Comorbidity, Clustering, Treatment differences	2	H: <200	H: ≥200	30-day
Fanaroff,	2009-	Cross-	3,747,866	Median	68.1	Age, Severity,	3	H: <400	H: >800	In-hospital

First author, country (year)	Study period	Study design	Total population (patients or procedures)	Age	Male (%)	Risk adjustment	No. of groupings	Low volume definition (PCI procedures/ year)	High volume definition (PCI procedures/ year)	Mortality outcome
US (2017)[292]	2015	sectional		(IQR): 65 (56-74)		Comorbidity, Clustering, Treatment differences		O: <50	O: >100	
Fanaroff, US (2018)[293]	2009-2014	Cross-sectional	723,644	Median (IQR): 74 (69-80)	62	Age, Severity, Comorbidity, Clustering, Treatment differences	3	O: <50	O: >100	In-hospital, 30-day and 1 year
Hulme, England and Wales (2018)[271]	2013-2014	Retro-spective cohort study	133,970	Mean ± SD: 65.1 ± 12.1	74.3	Age, Sex, Severity, Comorbidity, Hospital characteristics, Clustering, Treatment differences	2	O: < 75	O: ≥75	In-hospital and 30-day
Inohara, Japan (2017)[299]	2014-2015	Cross-sectional	323,322	Mean ± SD: 70.0 ± 11.0	76	Age, Sex, Severity, Comorbidity	10	H: ≤149 O: ≤23	H: ≥778 O: ≥134	In-hospital
Kim, South Korea (2013)[304]	2003-2004	Retro-spective cohort study	44,363	Mean age ± SD: 63.8 ± 10.2	64.9	Age, Sex, Severity, Comorbidity, Treatment differences	3	H: <200	H: ≥400	30-day
Kodaira, Japan (2018)[298]	2010-2015	Cross-sectional	14,437	Mean ± SD: 67.7 ± 11.1	79.6	Age, Severity, Comorbidity, Clustering	2	H: <200	H: ≥200	In-hospital

First author, country (year)	Study period	Study design	Total population (patients or procedures)	Age	Male (%)	Risk adjustment	No. of groupings	Low volume definition (PCI procedures/ year)	High volume definition (PCI procedures/ year)	Mortality outcome
Kontos, US (2013)[294]	2006-2009	Cross-sectional	87,324	>70 years old: 24.2%	71.7	Age, Severity, Comorbidity, Treatment differences, (Hospital characteristics)*	3	H: ≤36 Primary PCI	H: >60 Primary PCI	In-hospital
Kubo, Japan (2019)[302]	2014-2016	Cross-sectional	17,549	Mean ± SD: 70.8 ±12.4	74.0	Age, Sex, Comorbidity, Severity, Treatment differences	4	H: <213	H: >497	In-hospital
Kumbhani, US (2009)[295]	2001-2007	Cross-sectional	29,513	Mean ± SD: 60.8 ± 13.1	71.4	Age, Sex, Comorbidity, Clustering, Hospital characteristics, (Treatment differences)*	3	H: ≤36 Primary PCI (<200 PCI Total PCI)	H: >70 Primary PCI (>400 Total PCI)	In-hospital
Kuwabara, Japan (2011)[300]	2006	Cross-sectional	8,391	Mean ± SD: 67.0 ± 12.1	75.8	Age, Sex, Severity, Comorbidity, Clustering, Treatment differences	4	H: ≤26 Primary PCI	H: ≥78 primary PCI	In-hospital
Navarese, Italy (2011)[305]	2005-2006	Cross-sectional	2,558	Median age between 59 and 64	77.8	Age, Sex, Severity, Comorbidity, Clustering, Hospital characteristics	2	H: ≤66 Primary PCI (if time-to-presentation ≤90 minutes)	H: >66 Primary PCI (if time-to-presentation ≤90 minutes)	In-hospital

First author, country (year)	Study period	Study design	Total population (patients or procedures)	Age	Male (%)	Risk adjustment	No. of groupings	Low volume definition (PCI procedures/ year)	High volume definition (PCI procedures/ year)	Mortality outcome
O'Neill, England and Wales (2017)[303]	2007-2013	Retro-spective cohort study	427,467	Mean ± SD: 64.9 ± 11.9	73.5	Age, Sex, Severity, Comorbidity, Clustering	6	H: ≤199	H: ≥2000	30-day
Qian, US (2019)[297]	2012-2015	Cross-sectional	144,196	60-69 years old: 30.8% 70-79 years old: 24.3% ≥ 80 years old: 12.5%	70.3	Age, Severity, Comorbidity, Clustering	2	H: <200 O: <50	H: ≥200 O: ≥50	30-day
Shiraishi, Japan (2008)[301]	2000-2005	Cross-sectional	1,785	Mean ± SD: 67.8 ± 12.3	73.6	Age, Sex, Severity, Comorbidity, Treatment differences	2	H: <36 Primary PCI	H: >36 Primary PCI	In-hospital
Srinivas, US (2009)[296]	2000-2002	Cross-sectional	7,321	Mean ± SD: 61.2 ± 13.0	71.4	Age, Sex, Severity, Comorbidity	2	H: ≤50 Primary PCI O: ≤ 10 Primary PCI	H: >50 Primary PCI O: > 10 Primary PCI	In-hospital
Xu, China (2016)[306]	2004-2011	Pro-spective cohort study	1,948	Mean ± SD: 59.9 ± 10.5	78.9	Age, Severity, Comorbidity, Treatment differences	2	O: <15 LM PCI Procedures per year for 3 consecutive years	O: ≥15 LM PCI Procedures per year for 3 consecutive years	30-day and 3 year

First author, country (year)	Study period	Study design	Total population (patients or procedures)	Age	Male (%)	Risk adjustment	No. of groupings	Low volume definition (PCI procedures/ year)	High volume definition (PCI procedures/ year)	Mortality outcome
Yu, Taiwan (2017)[307]	2009	Cross-sectional	34,193	Mean ± SD: 65.73 ± 12.24	73.4	Age, Comorbidity, Treatment differences, Hospital characteristics, (Clustering)*	2	H: <200 O: <50	H: ≥200 O: ≥50	30-day
Zahn, Germany (2008)[308]	2003	Cross-sectional	27,965	Mean ± SD: 65.7 ± 11.1	72.9	Age, Sex, Severity, Comorbidity, (Clustering)*	2	H: <325	H: >325	In-hospital

Key: H – hospital; O – operator; LM – left main; PCI – percutaneous coronary intervention; SD – standard deviation; IQR – interquartile range.

4.3.2.2 Study design

All included studies were observational, with the majority being cross-sectional in nature (n=17).[288-290, 292-296, 298-301, 305, 307, 308] The remainder were classified by study authors as either retrospective cohort (n=4)[271, 291, 303, 304] or prospective cohort (n=1).[306]

4.3.2.3 Study population

In total, 6,432,265 patients or procedures were included across 22 studies. Some studies counted the number of patients in the dataset, whereas others referred to the number of PCI procedures undertaken. However, more often than not, there was ambiguity as to whether it was the numbers of procedures or patients that were used to describe the study population.

Thirteen studies examined the volume-outcome relationship for patients undergoing PCI for any indication (henceforth referred to as total PCI),[271, 288, 290, 292, 293, 295, 297-299, 303, 304, 307, 308] eight studies examined this relationship in patients undergoing primary PCI.[271, 294-296, 300, 301, 303, 305] Nine studies focused on patients with some form of ACS (STEMI/Non-ST elevation myocardial infarction (NSTEMI) and or unstable angina (UA)) or emergent/urgent admission, with or without cardiogenic shock, regardless of whether primary PCI was performed or not.[271, 288, 290, 292, 293, 298, 299, 302, 308] Three studies focused on patients undergoing elective or non-emergent PCI procedures.[291, 297, 303] Two studies focused on patients undergoing multi-vessel PCI (MVPCI) procedures.[289, 290] Other populations of interest examined include those undergoing LMPCI procedures (n=1),[306] and patients with specific target lesion characteristics — CTO (n=1),[298] Type C (n=1)[298] or bifurcation (n=1).[298] Of the eight studies which reported the breakdown in emergent caseload (that is, those cases which were considered an emergency) between highest and lowest volume groupings,[288, 290, 292, 293, 298, 300, 308] six reported that the lowest volume groupings performed a disproportionately higher number of emergent procedures.[288, 290, 292, 293, 298, 308]

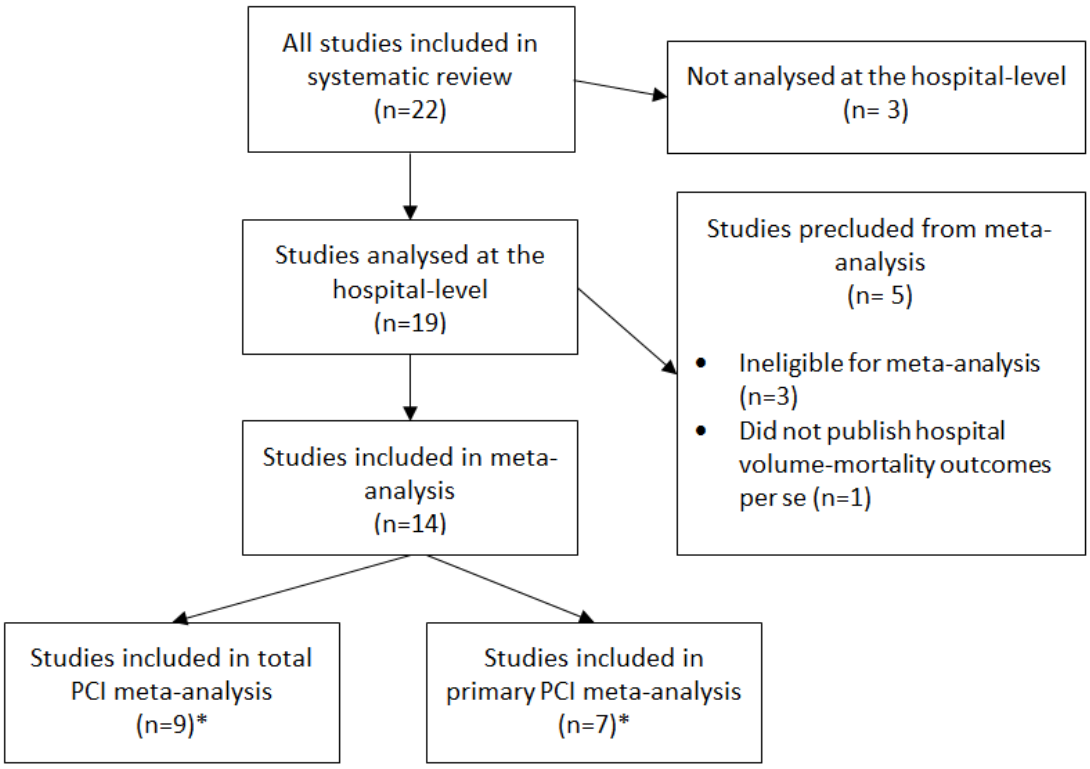
The studies reported median or mean ages of the study population; these ranged from 59[291] to 74 years.[293] The majority of included patients were male, with the proportion ranging from 62%[293] to 97.9% (in a study based in the US Veteran's Administration, which has predominantly male patients).[291] The majority of patients in the included studies underwent stenting as part of their PCI procedures, with values ranging from 60.9%[304] to 100%.[289, 290] The proportion of emergent procedures ranged from 0%[291] to 100%[294-296, 301, 305] and was largely influenced by the inclusion and exclusion criteria of the individual studies.

4.3.2.4 Level of analysis

Nineteen studies conducted the volume-outcome analysis at the hospital-level,[288-292, 294-305, 307, 308] with nine conducting the analysis at the individual operator-level.[271, 290, 292, 293, 296, 297, 299, 306, 307] Of the 22 studies, six conducted the analysis at both the hospital and operator level and investigated the interaction between hospital and operator volume on patient outcomes.[290, 292, 296, 297, 299, 307] One of these six studies only analysed findings at the hospital level to investigate the interaction between operator and hospital volume, and did not publish findings on the hospital-level volume relationship with mortality per se.[292] Meta-analyses were planned at both a hospital (total PCI and primary PCI) and at an operator level (total PCI and primary PCI) (Section 4.3.3). Six of the 22 studies did not report data suitable for inclusion in any of the planned meta-analyses,[288, 289, 291, 293, 302, 306] resulting in 16 includable studies (Figure 4.1).

Figure 4.2 illustrates the flow of studies included in the meta-analysis of hospital-level data. Fourteen of 19 studies that reported volume outcome data at a hospital level were included in the meta-analysis,[290, 294-301, 303-305, 307, 308] of which nine looked at total PCI[290, 295, 297-299, 303, 304, 307, 308] and seven looked at primary PCI. [294-296, 300, 301, 303, 305] Four studies were excluded from the meta-analysis as they did not have data suitable for inclusion in a meta-analysis;[288, 289, 291, 302] one study that did not publish hospital-level outcomes per se was also excluded.[293]

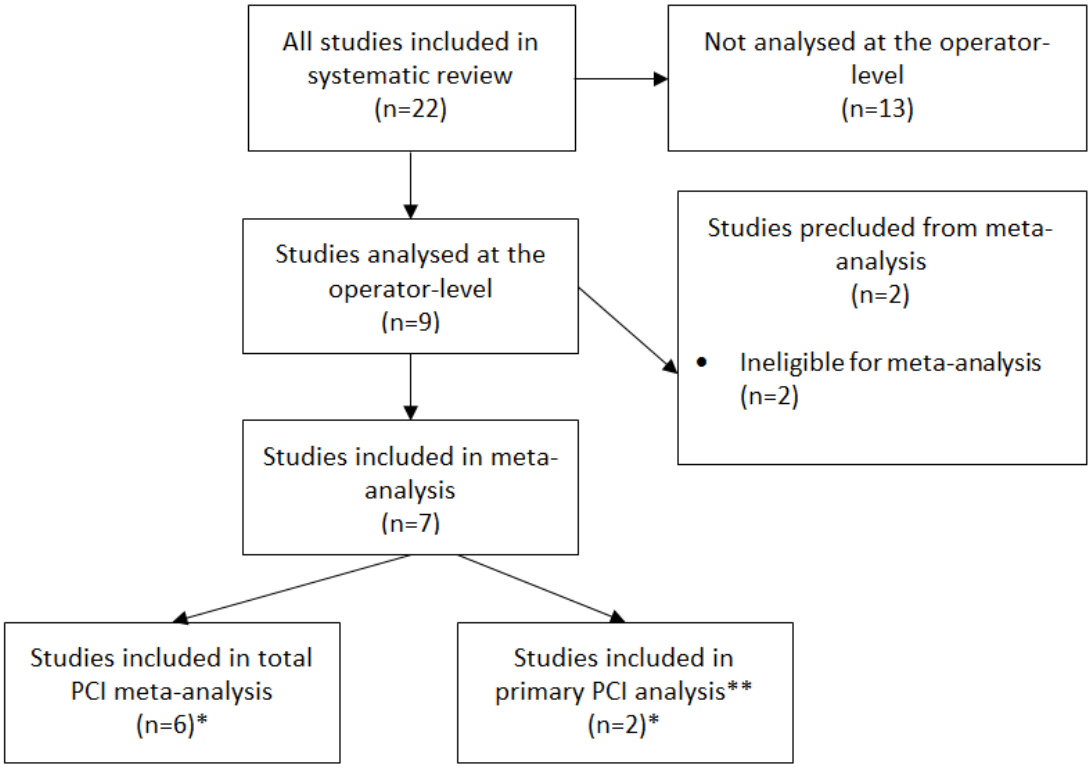
Figure 4.2: Flow diagram of hospital-level studies



* Two studies included in both meta-analyses.

Of the nine studies conducted at the operator level, the removal of two studies not eligible for inclusion due to the lack of suitable data,[293, 306] resulted in seven studies being included in our final meta-analyses models.[271, 290, 292, 296, 297, 299, 307] These seven studies are further divided into those looking at total PCI (n=6)[271, 290, 292, 297, 299, 307] and those looking specifically at primary PCI (n=2).[271, 296] One study examined both total and primary PCI volume (Figure 4.3).[271]

Figure 4.3: Flow diagram of operator-level studies



* One study included in both analyses.
** Meta-analysis not considered appropriate to conduct.

3.3.2.1 Data source

Twelve of the included studies obtained data from clinical databases,[292, 294-299, 301, 302, 305, 306, 308] seven obtained data from administrative databases,[288-291, 300, 304, 307] while three studies obtained data from linked clinical and administrative databases.[271, 293, 303]

4.3.2.5 Study period

While the review was limited to studies published in 2008 or later, the age of the data used in the studies varied greatly. The oldest data included came from three studies whose data collection commenced in 2000: Adogwa et al. (2000-2005),[288] Shiraishi et al. (2000-2005)[301] and Srinivas et al. (2000-2002).[296] The study with the most recent data is Kubo et al. which includes the study period 2014-2016.[302] The duration of studies also varied greatly, ranging from six months[300] to eight years.[306]

4.3.2.6 Risk adjustment

To meet inclusion criteria, all studies were required to report adjusted outcomes, controlling for important confounding factors that may have biased the results (Table 4.1). Fourteen of the 22 included studies adjusted for age, sex, severity of disease and comorbidity.[271, 288-291, 296, 299-305, 308] In line with the approach taken by researchers who published a 2010 systematic review on this topic, case-mix adjustment was considered incomplete if the study did not, as a minimum, adjust for all four of these variables.[9] However, several included studies did not include sex as a variable in the regression models,[292-294, 297, 298] and instead referred to a prediction model created by a team of researchers specifically for predicting the risk of mortality post-PCI, in an American population.[309] This analysis found that sex was no longer significantly associated with mortality after adjusting for multiple potential confounders.[309] Therefore studies which were considered to be incompletely adjusted were not excluded, but were analysed in subgroup analyses to examine the impact of incomplete adjustment on the overall pooled effect estimate (Appendix 8).

Fourteen studies reported in-hospital mortality as an outcome,[288-290, 292, 294-296, 298-302, 305, 308] five studies reported 30-day mortality,[291, 297, 303, 304, 307] one reported both in-hospital and 30-day mortality,[271] one study reported in-hospital, 30-day and one-year mortality,[293] and one study reported 30-day and three-year mortality.[306] No study reported survival (for a minimum of three months) as an outcome.

4.3.2.7 Definition of high- and low-volume hospitals/operators

Definitions of high and low volume varied widely between studies, and sometimes without a clear rationale. Some studies developed thresholds that were predominantly data-driven[289, 290, 296, 299, 300, 302, 305, 308] (for example, dividing the population into two or more equal sized groups (quantiles)), others developed thresholds that were predominantly guideline-driven[271, 291-295, 297, 298, 301, 303, 304, 307] (for example, based on ACCF/AHA/SCAI guidelines),[11] while others did not provide a clear explanation.[288, 306]

Regarding total PCI, a high-volume hospital ranged from providing 200 or more PCI procedures per year[291, 297, 298, 307] to 2,000 or more procedures per year,[303] with a median value of 497 PCI procedures per year. Similarly, the definition of a low-volume hospital ranged from 149 or fewer PCI procedures per year[299] to 542 or fewer PCI procedures per year,[290] with a median value of 200 PCI procedures per year.

Regarding operator definitions, a high-volume operator ranged from those undertaking 50 or more PCI procedures per year[297, 307] to 134 or more PCI

procedures per year,[299] with a median value of at least 100. A low-volume operator ranged from those providing 15 or fewer PCI procedures per year[290] to 75 or fewer PCI procedures per year,[271] with a median value of 50.

For primary PCI, the definition of a high-volume hospital ranged from 36 or more primary PCI procedures per year[301] to 78 or more primary PCI procedures per year,[300] with a median value of at least 63. Definitions of low-volume hospitals ranged from 26 or fewer primary PCI procedures per year[300] to 66 or fewer primary PCI procedures per year,[305] with a median value of 36. One study used a threshold of >10 and ≤10 primary PCI procedures per year to define high- and low-volume operators, respectively, and dichotomised their data on this basis.[296]

Several studies also tested the effect of changing the threshold, or how the threshold/volume was calculated, on the overall outcome.[271, 292, 295-297, 300, 307, 308] Some of the alternative thresholds changed the results of the study,[296, 297, 308] indicating how shifting the threshold can impact the findings. Furthermore, how the volumes were grouped (tertiles, quartiles, and so on) also varied substantially between studies with the number of groupings ranging from two (n=10)[271, 291, 296-298, 301, 305-308] to 10 (n=1).[299]

The proportion of patients who underwent PCI procedures in low-volume hospitals or by low-volume operators varied substantially from study to study. The proportion of patients in low-volume hospitals for any PCI indication (total PCI) ranged from 0.6%[303] to 44.3%,[304] with a median proportion of 15.2%. The proportion ranged from 3.1%[271] to 26.7%,[307] with a median of 10% for low-volume operators (total PCI). For primary PCI procedures, the proportion provided in low-volume hospitals ranged from 0.07%[303] to 57.2%,[301] with a median of 14.2%. The proportion of patients who underwent primary PCI by low-volume operators was provided by only one study, and this was 28.5%.[296] In general, the proportion of care provided in low-volume settings or by low-volume providers decreased over time. When comparing the oldest with the newest studies, the proportion of care provided in low-volume settings decreased from: 20.6%[308] to 2.1%[297] for total PCI procedures and 57.2%[301] to 0.07%[303] for primary PCI procedures (Table A.10). The proportion of care provided by low-volume operators decreased from 25%[290] to 4.8%[297] for total PCI procedures.

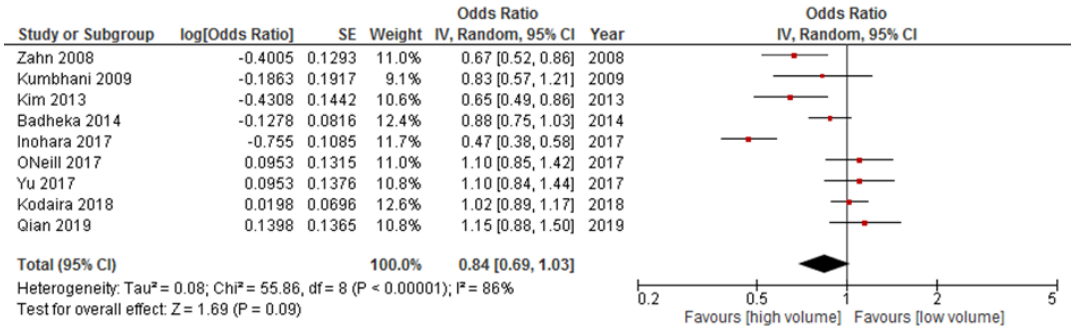
4.3.3 Primary outcomes

Postoperative mortality rates (aggregated at the study level) ranged from 0.9%[299] to 2.6%[271] following PCI procedures performed for any indication (that is, total PCI), with a mean mortality rate of 1.5%. Whereas for patients undergoing primary PCI procedures, postoperative mortality rates ranged from 3.2%[295] to 10.1%,[301] with a mean mortality rate of 5.3% (Appendix 3).

4.3.3.1 Total PCI at the hospital level

Nine studies investigated the relationship between hospital volume and mortality, for total PCI procedures (Figure 4.4).[290, 295, 297-299, 303, 304, 307, 308] No statistically significant difference was found in postoperative mortality between the highest and the lowest volume hospitals (odds ratio (OR): 0.84, 95% confidence interval (CI): 0.69-1.03). Of note, there was considerable heterogeneity (I^2 = 86%) across trials in the estimated pooled effect.

Figure 4.4: Results of the meta-analysis investigating the relationship between hospital volume and mortality, for total PCI procedures



Key: CI – confidence interval; IV – inverse variance; SE – standard error.

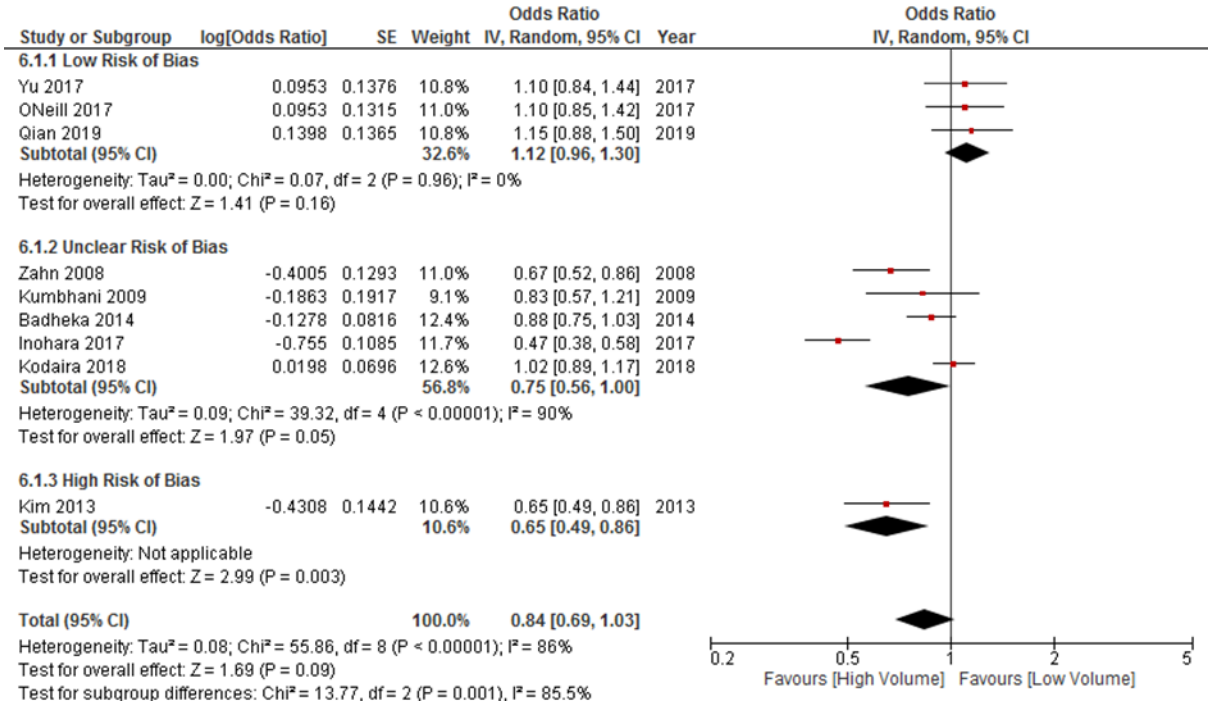
Exploratory random-effects meta-regression was conducted to explore potential causes of this heterogeneity, the results of which are available in Appendix 7 (Figure A.1-A.7). No obvious cause of heterogeneity was found, that is, no covariate reached statistical significance suggesting that a combination of factors may have contributed toward it. Caution however is advised when interpreting this finding due to the limited number of studies.

Subgroup analysis was conducted to examine the impact of the following factors on the overall pooled effect estimate: study risk of bias, region, completeness of case-mix, definition of low volume, study period and mortality outcome.

Subgroup analyses indicated that the overall pooled effect estimate was sensitive to risk of bias, as studies with a low risk of bias[297, 303, 307] (OR: 1.12, 95% CI: 0.96-1.30)

were significantly less likely (p = 0.001) to find a volume-outcome relationship compared with studies that had an unclear[290, 295, 298, 299, 308] (OR: 0.75, 95% CI: 0.56-1.00) or high risk of bias (OR: 0.65, 95% CI: 0.49-0.86) (Figure 4.5).[304] There was minimal heterogeneity within the low risk of bias subgroup (I^2 = 0%), however, there were only three studies within this subgroup.[297, 303, 307] There is no apparent reason why these three studies had similar effect sizes, but it may be related to the relatively small number of low-volume centres in these studies.[297, 303, 307]

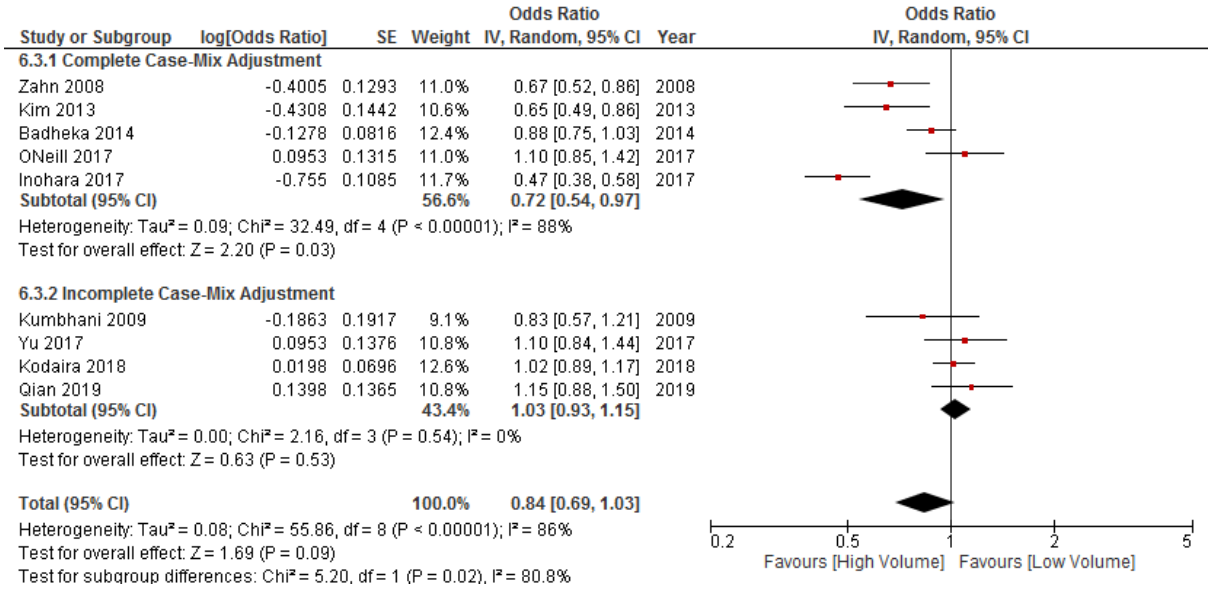
Figure 4.5: Subgroup analysis examining the distribution of pooled effect sizes according to the risk of bias of included studies



Key: CI – confidence interval; IV – inverse variance; SE – standard error.

The overall pooled effect estimate was also sensitive to the completeness of case-mix adjustment. Studies with complete case-mix adjustment (adjusted for age, sex, comorbidity and severity at a minimum) (OR: 0.72, 95% CI: 0.54-0.97) were significantly more likely (p=0.02) to find a volume-outcome relationship compared with studies with incomplete case-mix adjustment (OR: 1.03, 95% CI: 0.93-1.15) (Figure 4.6).

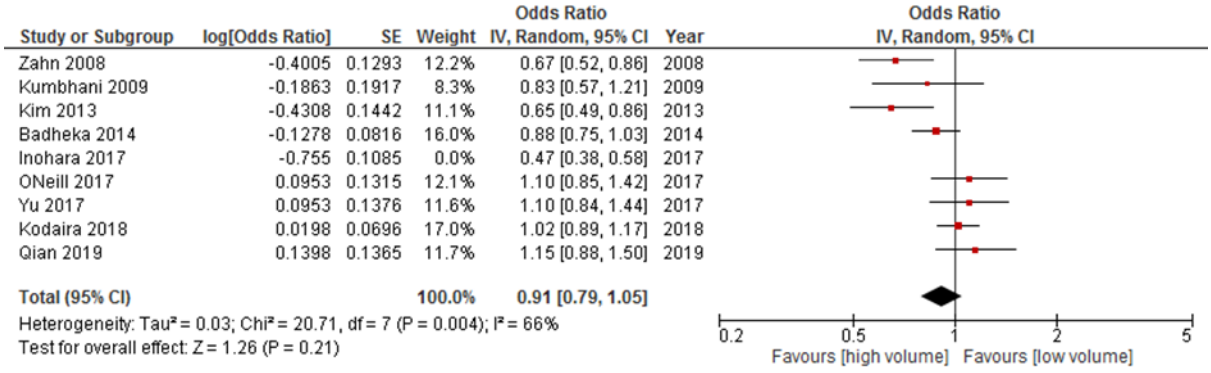
Figure 4.6: Subgroup analysis examining the distribution of pooled effect sizes according to the completeness of case-mix adjustment



The overall pooled effect estimate was not sensitive to the median study period for which the PCI data were derived, region, mortality outcome used, or the definition used for a low-volume hospital ($p > 0.05$).

Visual inspection of Figure 4.6 highlights that the study by Inohara et al. appears to be an outlier.[299] In contrast to other studies (which used a maximum of six groupings), the data in this study were divided into deciles of volumes and hence outcomes from extremely low- and high-volume hospital (≤149 vs. ≥778 PCI procedures per year) groupings were compared.[299] On exclusion of the study,[299] visual inspection of the forest plot indicates an apparent temporal trend (that is, with progression of the year of study publication). The pooled effect estimate is still not significant (OR: 0.91, 95% CI: 0.79-1.05) and the level of heterogeneity also decreases, though it is still substantial (I^2 = 66%) (Figure 4.7).

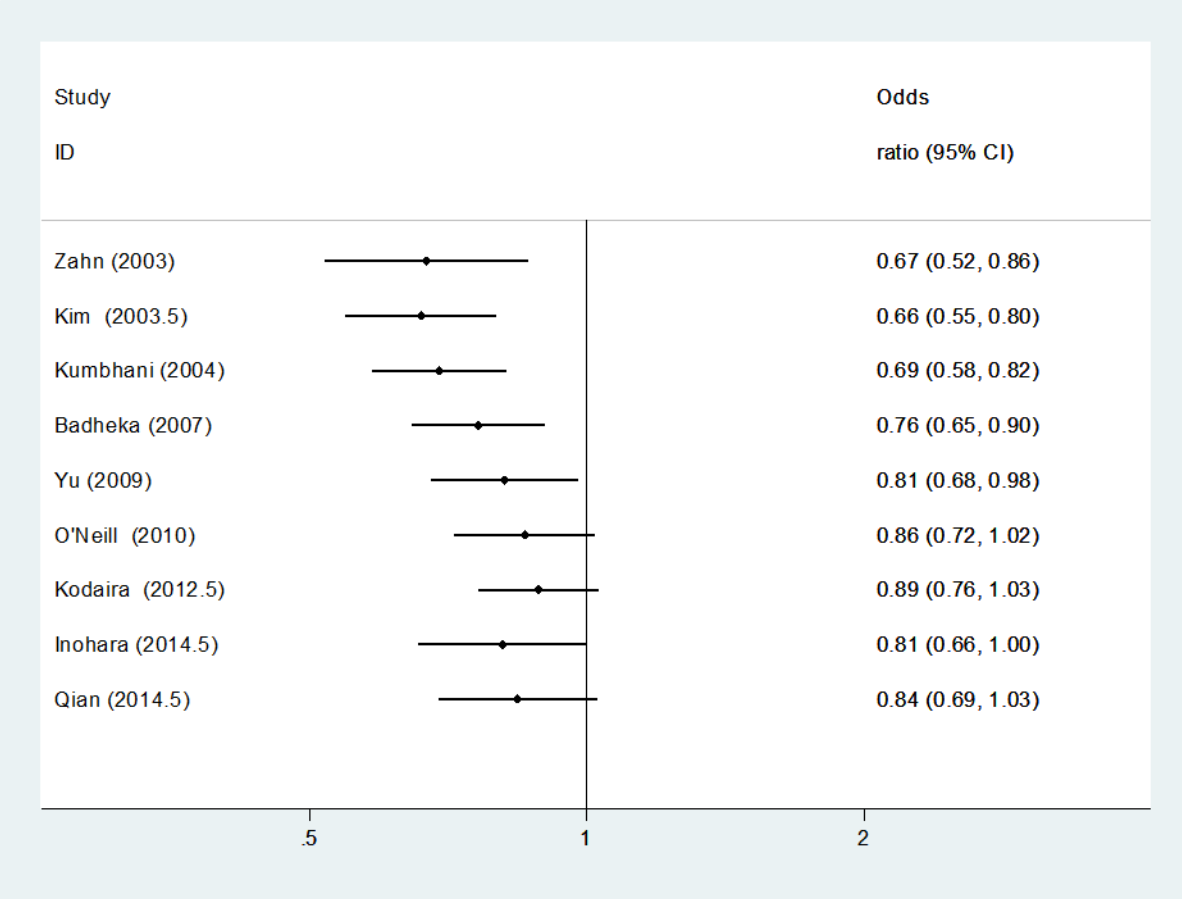
Figure 4.7: Results of the sensitivity analysis investigating the relationship between hospital volume and mortality, for all PCI procedures, when Inohara et al. is excluded



Key: CI – confidence interval; IV – inverse variance; SE – standard error.

The temporal trend is more evident when a cumulative meta-analysis was conducted, using the median year of data collection for each study as opposed to the study publication year (Figure 4.8). Here we can observe a gradual change in the pooled effect estimate shifting from a 33% reduction in the odds of mortality (OR: 0.67, 95% CI: 0.52-0.86) in high volume compared with low volume hospitals when limited to the earliest study data[308] to a 16% reduction (OR: 0.84, 95% CI: 0.69-1.03) when data from the most recent studies are included.[297] Notably, we can see that the difference is no longer statistically significant when study data from the year 2010 onwards is included.[303]

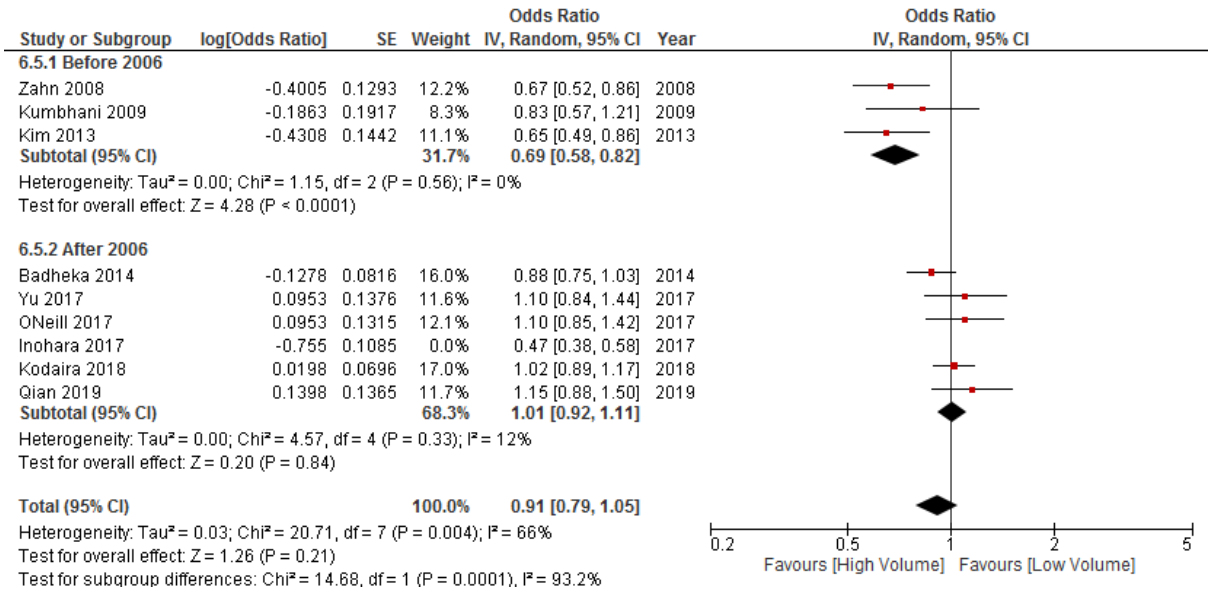
Figure 4.8: Cumulative meta-analysis investigating the relationship between hospital volume and mortality, for total PCI procedures



Key: CI – confidence interval.

The outlier effect of Inohara et al. is particularly evident when the subgroup analysis for study period is re-examined without this study,[299] as a statistically significant difference (p=0.0001) can now be seen between studies with a median study period prior to 2006 (OR: 0.69, 95% CI: 0.58-0.82) compared with those with a median study period of 2006 or later (OR: 1.01, 95% CI: 0.92-1.11). Heterogeneity across trials remains substantial (I^2 = 66%) (Figure 4.9).

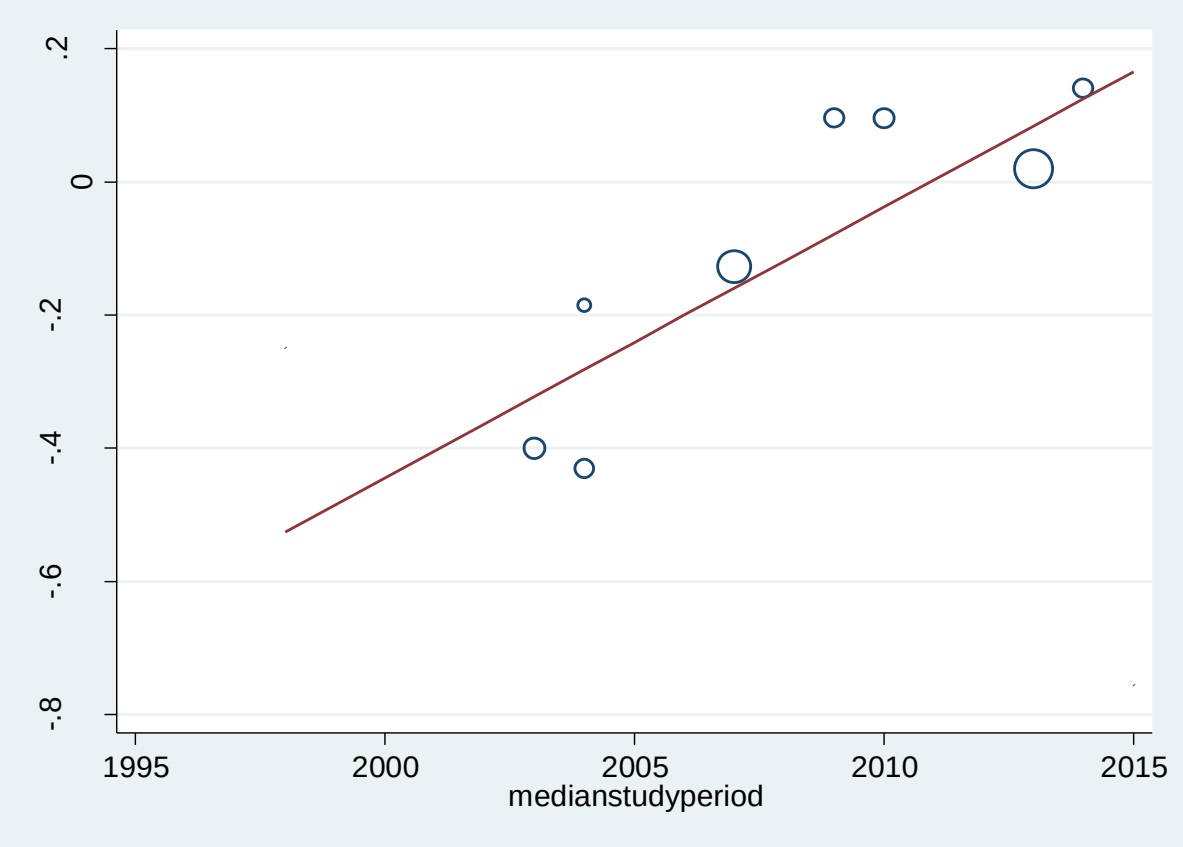
Figure 4.9: Sensitivity analysis without Inohara et al. for study period



Key: CI – confidence interval; IV – inverse variance; SE – standard error.

Furthermore, repeating the meta-regression analysis without Inohara et al. indicates that all of the between-study variation may be explained by the median study period (p=0.008 for moderator effect)) (Figure 4.10). There is an apparent temporal trend with the effect size diminishing (higher log odds ratio value means a lower effect size) as the median year of study data progresses. The significant moderator effect (p=0.008) of the covariate (that is, median study period) on the dependent variable (that is, effect size) is evident by the change in residual heterogeneity (that is, the I^2 values) when the meta-regression is conducted without any covariates (I^2 = 66.2%) compared with when the covariate is included in the model (I^2 = 0%) for the eight observations. As numerous meta-regressions were undertaken, the analysis is impacted by multiple hypothesis testing. In this case, using Bonferroni, the p-value for statistical significance can be adjusted to 0.007 and the observed effect of median study period is no longer statistically significant. Caution should therefore be applied in interpreting the results of this analysis.

Figure 4.10 Meta-regression plot examining relationship between median study period and the log of the effect size for high PCI volume hospitals, without Inohara et al.



Key: logOR totalhosp – log of the odds ratio; medianstudyperiod – median study period

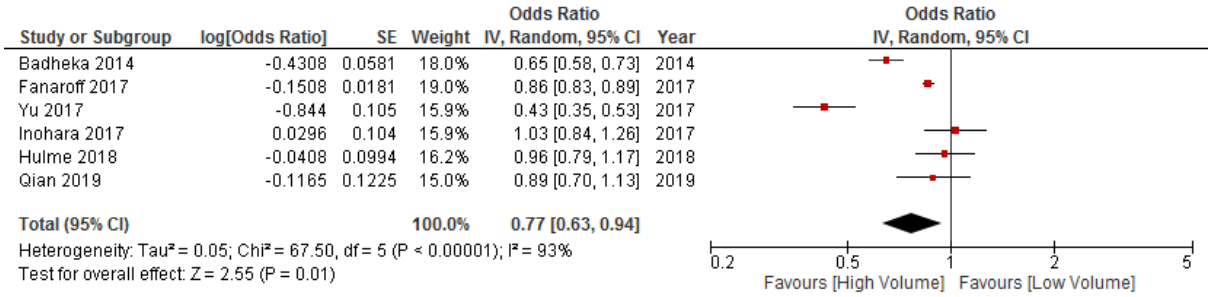
Sensitivity analyses were also conducted to investigate the impact of individual studies and alternative thresholds (defining high and low volume) on the overall pooled effect estimate (Appendix 8, Figures A.20-A.28). Some studies investigated the impact of using alternative volume thresholds on mortality.[297, 307, 308] It was found that the overall pooled effect estimate remains non-significant under all sensitivity analysis scenarios, except when a threshold of 400 PCI procedures per year or higher (OR: 0.82, 95% CI: 0.69-0.99) was used.[297] Notably, this study by Qian et al. tested a range of thresholds from 200 to 1,000 PCI procedures per year (Figures A.33-A.36).

4.3.3.2 Total PCI at the operator level

Six studies investigated the relationship between operator volume and mortality, for all PCI procedures.[271, 290, 292, 297, 299, 307] Figure 4.11 depicts the forest plot of these six studies. The pooled effect estimate was found to be significantly in favour of high-volume operators (OR: 0.77, 95% CI: 0.63-0.94). That is, high-volume operators were associated with a 23% reduction in the odds of in-hospital or 30-day

mortality compared with low-volume operators. However the analysis of the pooled effect sizes had considerable levels of heterogeneity (I^2 = 93%).

Figure 4.11: Results of the meta-analysis investigating the relationship between operator volume and mortality, for all PCI procedures



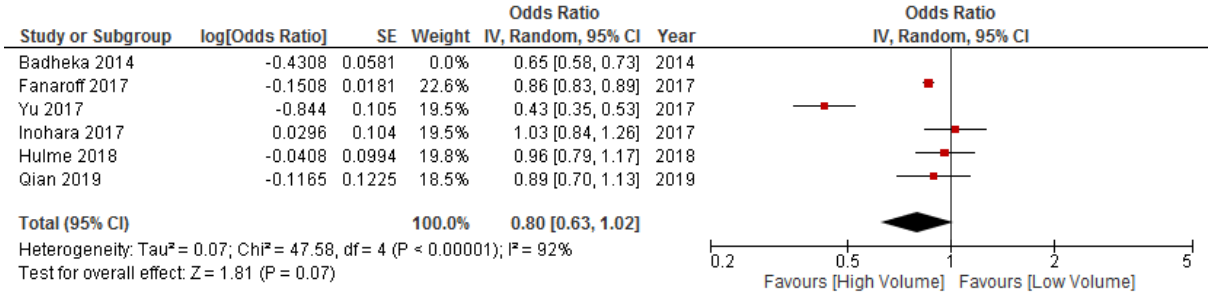
Key: CI – confidence interval; IV – inverse variance; SE – standard error.

Exploratory random-effects meta-regression was conducted to explore potential causes of this heterogeneity. No covariate reached statistical significance suggesting that a combination of factors may have contributed towards the considerable level of heterogeneity. Results of the exploratory meta-regression are available in Appendix 7 (Figures A.8-A.12).

Subgroup analyses indicated that the overall pooled effect estimate was not sensitive to risk of bias, region, mortality outcome used, completeness of case-mix adjustment or definition of low-volume operators ($p > 0.05$). However due to the limited number of included studies, it was likely underpowered to detect an effect. All studies were conducted after 2006, so it was not appropriate to do any subgroup analysis according to this cut-off year (Appendix 8, Figures A.49-A.57).

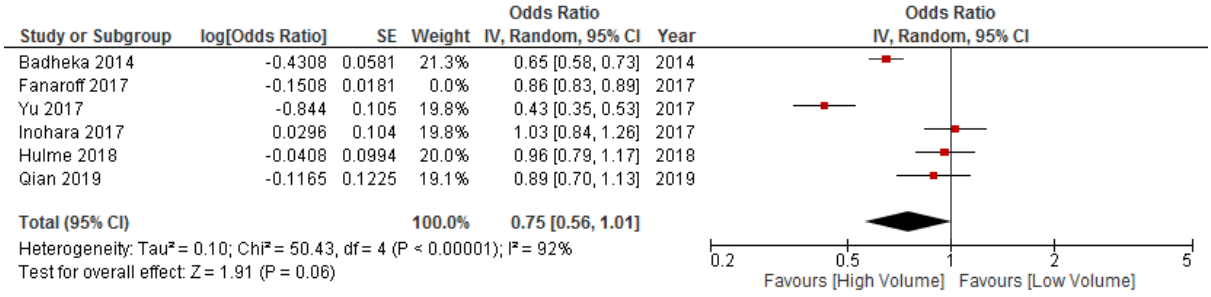
In sensitivity analyses each study was removed one-by-one to examine the effect on the overall pooled effect estimate (Appendix 8, Figures A.43-A.48). The relationship between operator volume and outcome remains significant except when the studies by Badheka et al.[290] and Fanaroff et al.[292] are removed (OR: 0.80, 95% CI: 0.63-1.02, and OR: 0.75, 95% CI: 0.56-1.01, respectively) indicating the strong influencing effect of these large population-based studies (n=457,498 and n=3,747,866, respectively) (Figure 4.12 and Figure 4.13). While it would appear that the study by Yu et al. is an outlier due to its significantly large effect size (OR: 0.43, 95% CI: 0.35-0.53), the reasons for its outlier status are not clear.[307]

Figure 4.12: Results of the meta-analysis investigating the relationship between operator volume and mortality, for all PCI procedures, when Badheka et al. is excluded



Key: CI – confidence interval; IV – inverse variance; SE – standard error.

Figure 4.13: Results of the meta-analysis investigating the relationship between operator volume and mortality, for all PCI procedures, when Fanaroff et al. is excluded



Key: CI – confidence interval; IV – inverse variance; SE – standard error.

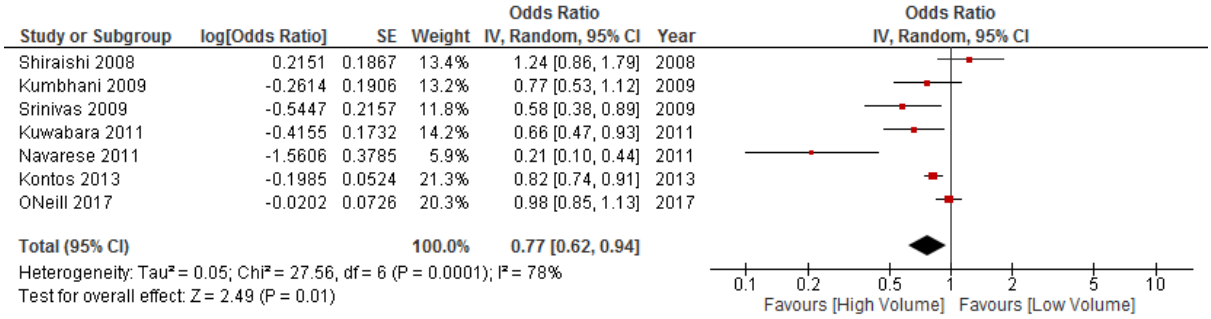
Some studies also investigated the impact of using alternative volume thresholds on mortality.[271, 292, 297, 307] However, the overall pooled effect estimate for the meta-analysis did not change when each of the outcomes from the different thresholds were entered into the model in turn (Appendix 8, Figures A.53-A.56).

4.3.3.3 Primary PCI at the hospital level

Seven studies investigated the relationship between hospital volume and mortality, specifically for primary PCI procedures.[294-296, 300, 301, 303, 305]

Figure 4.14 depicts the forest plot of these seven studies. The pooled effect estimate was found to be significantly in favour of high-volume hospitals (OR: 0.77, 95% CI: 0.62-0.94). That is, high-volume primary PCI hospitals were associated with a 23% reduction in the odds of in-hospital or 30-day mortality compared with low-volume hospitals. However, the analysis of the pooled effect sizes had considerable levels of heterogeneity (I^2 = 78%).

Figure 4.14: Results of the meta-analysis investigating the relationship between hospital volume and mortality, for primary PCI procedures

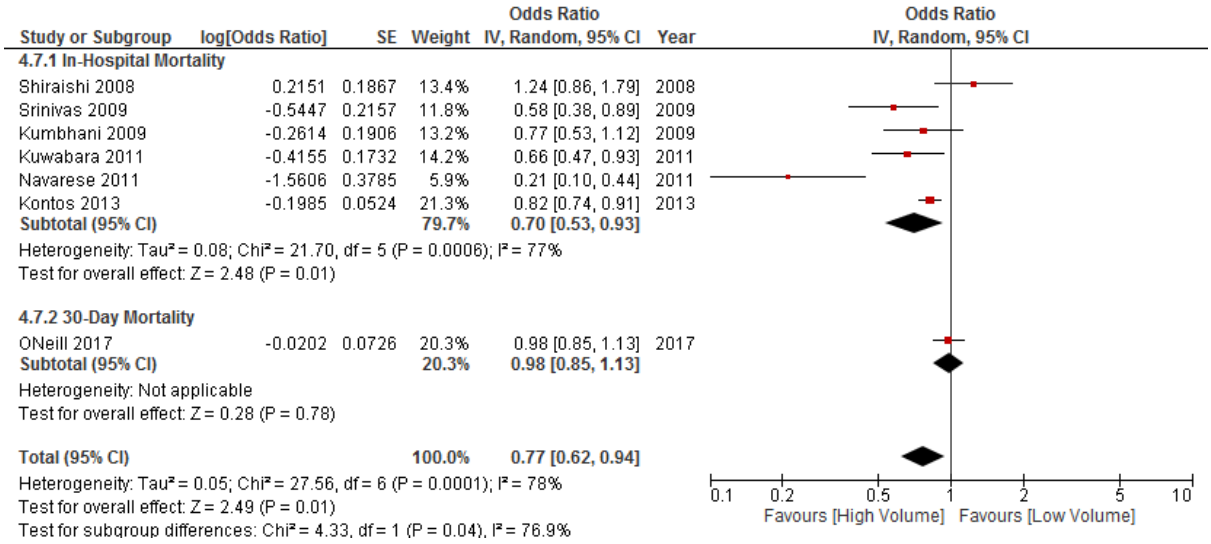


Key: CI – confidence interval; IV – inverse variance; SE – standard error.

Exploratory random-effects meta-regression was conducted to explore possible causes of this heterogeneity. No covariate reached statistical significance suggesting that a combination of factors may have contributed towards the considerable level of heterogeneity. Results of the exploratory meta-regression are available in Appendix 7 (Figures A.13-A.19).

Subgroup analyses indicated that the overall pooled effect estimate was not sensitive to study risk of bias, study period, region, completeness of case-mix adjustment, adjusted/unadjusted odds or definition of low-volume hospitals ($p > 0.05$) (Appendix 8). However due to the limited number of included studies, it was likely underpowered to detect an effect. Subgroup analyses indicated that the overall pooled effect estimate was sensitive to the mortality outcome used, as the single study which reported 30-day mortality[303] (OR: 0.98, 95% CI: 0.85-1.13) was significantly less likely ($p = 0.04$) to find a volume-outcome relationship compared with those which reported in-hospital mortality[294-296, 300, 301, 305] (OR: 0.70, 95% CI: 0.53-0.93) (Figure 4.15). However, as only one study in this meta-analysis used 30-day mortality rates, caution is needed when interpreting the findings of this subgroup analysis.

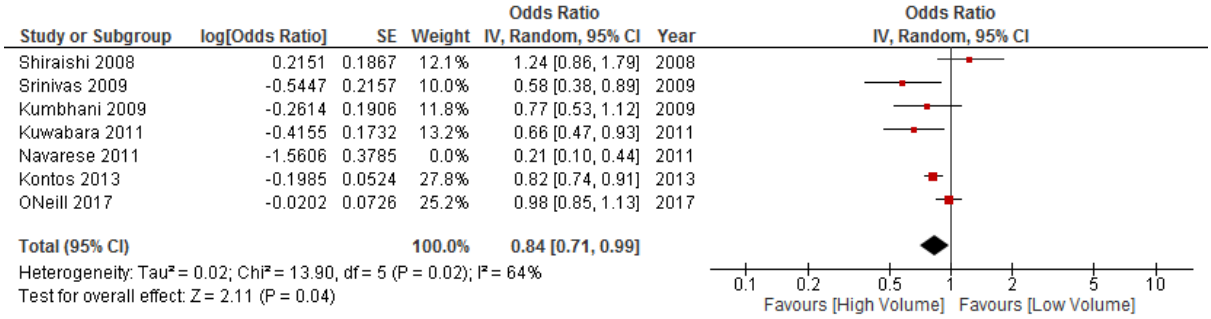
Figure 4.15: Subgroup analysis examining the distribution of pooled effect sizes according to the mortality outcome used



Key: CI – confidence interval; IV – inverse variance; SE – standard error.

Visual inspection of Figure 4.15 highlights that the study by Navarese et al. appears to be an outlier, and is possibly contributing most to the considerable heterogeneity.[305] This study may be considered an outlier as STEMI participants were only included in the model if time-to-presentation was 90 minutes or less (hence representing a subpopulation who would benefit most from primary PCI). Excluding this study in a sensitivity analysis did not substantially change the overall pooled effect estimate (OR: 0.84, 95% CI: 0.71-0.99), heterogeneity was reduced, but remained substantial (from an I^2 of 78% to an I^2 of 64%) (Figure 4.16).[305] Furthermore, sensitivity analyses removing each study in turn did not change the significance of the overall pooled effect estimate, nor did using outcomes from the alternative volume thresholds tested in three studies (Appendix 8, Figures A.58-A.68).[295, 296, 300] This suggests that the overall pooled effect estimate for primary PCI at the hospital level may have a greater degree of certainty around its results than that of both hospital level and operator level for total PCI.

Figure 4.16: Results of the meta-analysis investigating the relationship between hospital volume and mortality, for primary PCI procedures, when Navarese et al. is excluded



Key: CI – confidence interval; IV – inverse variance; SE – standard error.

4.3.3.4 Primary PCI at the operator level

Only two studies investigated the relationship between primary PCI at the operator level and mortality.[271, 296] Due to the low number and the conflicting findings reported by the studies, it was considered inappropriate to combine them in a meta-analysis.

Both studies were judged to be at a low risk of bias. The study by Srinivas et al. was conducted in New York State in the US and included PCI procedures undertaken between 2000 and 2002, with 7,321 patients and ranging from 1 to 55 procedures per operator.[296] The odds of mortality were found to be 34% lower (OR: 0.66, 95% CI: 0.48-0.91) for procedures undertaken by operators completing more than 10 primary PCI procedures per year compared with those undertaken by operators who performed 10 or fewer primary PCI procedures per year.[296] However, a larger (n=133,970) study based on more recent data (2013-2014) by Hulme et al. conducted across all public hospitals in England and Wales found no significant association between operator volume (at a threshold of 75 total PCI procedures per year) and mortality following primary PCI (OR: 0.93, 95% CI: 0.72-1.20).[271] Although different outcome measures were used for both studies, the more recent study by Hulme et al.[271] was associated with a lower overall mortality rate (30-day mortality of 2.6% vs. in-hospital mortality of 3.7% reported by Srinivas et al.), potentially reflecting secular improvements in the management of myocardial infarction (MI).[310]

4.3.3.5 Interaction between operator and hospital

Six studies examined the interaction between operator and hospital volume.[290, 292, 296, 297, 299, 307] Five studies reported that low-volume operators in low-volume hospitals were associated with the highest rate of mortality compared with high-volume operators in high-volume hospitals.[290, 292, 296, 299, 307] However, Qian et al. did not

detect any statistically significant difference between any combination of high- and low-volume operators and hospitals compared with the reference group (low-volume operators in low-volume hospitals).[297] The authors of three of these studies suggested that operator volume may be more important than hospital volume.[290, 296, 307] In other words, a high operator volume may offset the negative effects of a low-volume hospital, although the authors concluded that more research was required to confirm this interaction.

4.3.3.6 Minimum volume threshold

Ten studies reported a threshold above which the adjusted odds ratio for mortality became non-significant.[290, 292, 294, 296, 299, 300, 304, 305, 307, 308] For total PCI hospital volume,[299, 304, 308] these values ranged from 208[299] to 400.[304] For total PCI operator volume,[290, 292, 307] these values ranged from 15[290] to 100.[292] For primary PCI hospital volume,[294, 296, 300, 305] these values ranged from 36[294] to 66.[305] Only one study, which was conducted in the US, found a significant relationship between volume and outcome for primary PCI operator volume.[296] In this study, the a priori selected dichotomous threshold was 10 primary PCI procedures per year, and the mean number of primary PCI procedures conducted per operator per year was four and 19 in the low- and high-volume groups, respectively.[296] However, several studies found a bidirectional relationship, with intermediate groupings experiencing better or worse outcomes than their adjacent groupings.[288, 299, 302]

Six studies conducted spline analysis to investigate the dynamic relationship between volume and outcome, in an attempt to determine an appropriate minimum volume threshold.[271, 290, 292, 296, 299, 305] The thresholds varied hugely between studies. For example, with regards to total PCI hospital volume, Badheka et al. calculated a threshold of approximately 1,000 annual procedures in an American population,[290] whereas Inohara et al. calculated a much lower threshold of approximately 100 annual procedures in a Japanese population.[299] Notably, this study by Inohara et al. reported that low-volume hospitals that conduct 200 or fewer PCI procedures annually constitute over 80% of the hospitals providing PCI in Japan.[299] Qian et al. tested the volume-outcome relationship at multiple thresholds and attempted to determine an optimal threshold from the standpoint of the lowest p value. The authors calculated an optimal threshold of 900 total PCI procedures per year for hospitals (p=0.004) and 225 total PCI procedures per year for operators (p=0.0105). However the authors commented that these thresholds are unrealistically high and the added short-term mortality benefit from these elevated volumes is minimal.[297]

Due to the inconsistency in how thresholds were selected and compared, the bidirectional relationship found in some studies and the population-specific nature of spline analysis, it is not possible to state with any degree of certainty a minimum

volume standard for hospitals or operators when performing PCI for any indication or indeed primary PCI.

4.3.3.7 Long-term mortality outcomes

Only two studies, by Fanaroff et al.[293] and Xu et al.,[306] investigated the relationship between operator volume and long-term (that is, greater than 30 days) primary outcomes (Table A.10).[293, 306] No study investigated the relationship between hospital volume and long-term outcomes. After adjustment for confounders, the studies found that there was no significant difference in mortality between high- and low-volume groupings at one (HR: 1.04, 95% CI: 1.00-1.08)[293] or three (HR: 0.70, 95% CI: 0.45–1.11)[306] years post procedure. Notably, both studies had found significant differences in mortality between high- and low-volume groups at in-hospital[293] and 30-day time-points (Appendix 3).[293, 306] Therefore, it would appear that the volume-outcome relationship attenuated over time in these studies.

4.3.3.8 Mortality in specific patient subpopulations

The volume-outcome relationship within specific patient subpopulations was inconsistent. Two studies examined the volume-outcome relationship in patients undergoing elective PCI, with no significant difference observed between the high- and low-volume groupings at a hospital level[291, 303]. A significant inverse relationship between operator[290] or hospital[302] volume and mortality was observed in subgroups of patients presenting with cardiogenic shock on admission in two studies. Additionally, a significant inverse relationship between hospital volume and mortality was observed in a subgroup undergoing non-elective PCI (emergency or urgent PCI).[299] Furthermore, within ACS subpopulations (including various combinations of STEMI, NSTEMI and unstable angina), a significant inverse relationship between volume and mortality was generally observed within the short term (that is, in-hospital or 30-day mortality).[290, 292, 293, 295, 299] However, one study did not find a significant relationship between hospital volume and mortality in patients presenting with cardiogenic shock on admission (OR: 1.14, 95% CI: 0.98-1.32).[294] Similarly, a recent study did not find any significant relationship between operator (OR: 1.15, 95% CI: 0.85-1.56) or hospital volume (OR: 0.61, 95% CI: 0.22-1.73) and 30-day mortality in a STEMI subpopulation.[297] Moreover, the positive relationship in favour of high-volume groupings was found to be attenuated over time in all ACS subpopulations in a study by Fanaroff et al. which reported mortality outcomes at one-year follow-up.[293] This study also found that this relationship attenuated earlier for the subgroup comprising patients with NSTEMI and unstable angina, so that at 30 days there was no longer a significant association between operator volume and outcome (HR: 0.97, 95% CI: 0.94-1.09), having been present at the end of the in-hospital period (HR: 0.87, 95% CI: 0.80-0.95). Furthermore, one recent UK study (data 2013-2014) by Hulme et al., with a large

population and a low risk of bias, found no statistically significant difference between high- and low-volume operators in patients with ACS in terms of in-hospital (OR: 1.01, 95% CI: 0.76–1.34) or 30-day mortality (OR: 1.09, 95% CI: 0.88-1.35).[271]

Two studies of unclear risk of bias examined the volume-outcome relationship for a subpopulation undergoing PCI for multi-vessel disease, using the same dataset (the US National Inpatient Sample).[289, 290] Arora et al., which included data from 2006 to 2011, found a statistically significant benefit in favour of high-volume hospitals (OR: 0.75, 95% CI: 0.56-0.99),[289] whilst Badheka et al., which included data from 2005 to 2009, found no association between volume and mortality at the operator level (OR: 0.80, 95% CI: 0.62–1.05).[290] Although the latter study did conduct most analyses at both the hospital and operator level, for this particular subpopulation the analysis was only conducted at the operator level. It is therefore not possible to explore potential inconsistencies.[290]

Kodaira et al. examined the volume-outcome relationship in a range of specific subpopulations (bifurcations, Type C lesions, CTO, STEMI), and found no significant relationship in any of these subgroup analyses.[298] However, this study was probably too small (n=14,437) to detect a true difference in any of these subpopulations, especially for the less common bifurcation (n=4,062), Type C (n=4,384) and CTO (n=971) lesions.

4.3.4 Secondary outcomes

A variety of secondary outcomes were reported across twelve studies.[289-295, 297-299, 302, 306] These included length of stay,[289, 290] door-to-balloon (DTB) time,[294, 295] re-admission,[291] bleeding,[292, 293, 302] dialysis,[292] recurrent MI,[293, 306] unplanned revascularisations,[293, 306] inappropriate use of PCI,[297] and a range of composite outcomes including major adverse cardiac events (MACE) (Appendix 3).[271, 289, 290, 293, 298, 299, 306] The association between procedural volume and these secondary outcomes was mixed and is described below under 'Complications of PCI' and 'Healthcare utilisation and process outcomes'.

4.3.4.1 Complications of PCI

A range of composite outcomes were measured in seven studies.[271, 289, 290, 293, 298, 299, 306] Major adverse cardiac events (MACE), is a composite outcome which has been inconsistently defined in the literature,[311] but defined as a composite of death, MI, or unplanned revascularisation and measured in two of the included studies.[271, 293] Both studies found no significant relationship between operator volume and MACE, with Fanaroff et al. focusing on total PCI at one-year follow-up (HR: 1.01, 95% CI: 0.99–1.04)[293] while Hulme et al. analysed both total PCI population (OR: 1.13, 95% CI: 0.92–1.38) and primary PCI (OR: 1.24, 95% CI: 0.95–1.61) at

discharge.[271]

Arora et al. evaluated a composite of mortality or any complications (defined as post-procedure haemorrhage requiring blood transfusion, iatrogenic cardiac complications (including post-procedural MI and post-procedural need for revascularisation), pericardial complications, requiring open heart surgery, other iatrogenic respiratory complications (which included ventilator associated pneumonia, post-procedure aspiration pneumonia, and other respiratory complications not elsewhere classified), post-procedural stroke or transient ischemic attack, and other vascular complications) in a MVPCI population and found no significant relationship between hospital volume and this composite outcome (OR: 0.91, 95% CI: 0.80-1.05).[289]

Badheka et al.[290] defined this composite outcome of in-hospital mortality and any complications in a very similar manner to Arora et al.[289] and found a significant relationship between operator volume and this composite outcome in favour of high-volume operators (OR: 0.61, 95% CI: 0.58–0.63), but found no significant relationship at the hospital level (OR: 1.02, 95% CI: 0.93–1.12). Conversely, Inohara et al. found a statistically significant inverse relationship between hospital volume and a composite of in-hospital mortality and any complications (defined as tamponade, shock requiring mechanical and or inotropic support, stent thrombosis, emergency surgery and bleeding requiring transfusion) (OR: 0.49, 95% CI: 0.43-0.56).[299] However, this same study found no significant association between operator volume and this composite outcome (OR: 1.0, 95% CI: 0.89-1.13),[299] in direct contradiction to the findings by Badheka et al.[290] However, these differences in findings may partially be explained by substantial differences in the population under investigation (American vs. Japanese), as well as the fact that Inohara et al.[299] divided the population into deciles of PCI volume with the lowest-volume group defined as groups providing fewer than 150 annual hospital procedures. By comparison, Badheka et al.[274] used quartiles with the lowest-volume group defined as those providing 542 or fewer annual hospital procedures.

Two more studies of unclear[298] and high risk of bias,[306] respectively, also investigated the relationship between procedural volume and composite outcomes. Kodaira et al. found no significant relationship between hospital volume and a composite outcome of in-hospital mortality and any general complication (defined as severe coronary dissection or perforation, MI after PCI, cardiac shock or heart failure, cerebral bleeding or stroke and bleeding complications).[298] Similarly, Xu et al. found no significant relationship between operator volume and a composite outcome of mortality or stroke at 30 days or three years in a cohort study following patients who underwent LMPCI in a Chinese hospital.[306]

Other PCI complication outcomes were measured individually including hospital re-admission,[291] bleeding,[292, 293, 302] dialysis,[292] recurrent MI,[293, 306] and unplanned revascularisations.[293, 306] No significant volume-outcome relationships were observed for any of these outcomes, except for dialysis in a single study by Fanaroff et al.,[292] and access-site bleeding in another study by Kubo et al.[302] Fanaroff et al. reported that the post-operative requirement for dialysis was significantly higher when the PCI procedure was performed by lower (<50 PCI procedures annually) compared with higher (>100 PCI procedures annually) volume operators (>100 PCI procedures annually) (OR: 1.09, 95% CI: 1.01-1.17).[292] Kubo et al. reported that the odds of access site bleeding was significantly lower in high-volume (> 1490 procedures over three years) compared with low-volume hospitals (<640 procedures over three years) (OR: 0.69, 95% CI: 0.47-0.99), but that there was no association between hospital volume and non-access site bleeding (OR: 0.78, 95% CI: 0.49-1.25).[302]

4.3.4.2 Healthcare utilisation and process outcomes

Unlike the mixed evidence found for the relationship between procedural volume and PCI complications described above, there appeared to be a consistently significant relationship between procedural volume and healthcare utilisation or process outcomes, in favour of high-volume operators and hospitals.[289, 290, 294, 295]

Two large American studies, both of unclear risk of bias, found that high-volume operators and hospitals were both significantly associated with a reduced length of hospital stay.[289, 290] Arora et al. found that high-volume hospitals were associated with a hospital stay reduction of 0.31 days (95% CI: 0.42 to 0.20 fewer days) compared with low-volume hospitals.[289] Similarly, Badheka et al. found that both high-volume hospitals (logarithmic scale, OR: 0.95, 95% CI: 0.94-0.96) and high-volume operators (logarithmic scale, OR: 0.95, 95% CI: 0.94-0.95) were associated with shorter length of hospital stays, compared with low-volume hospitals and operators, respectively.[290]

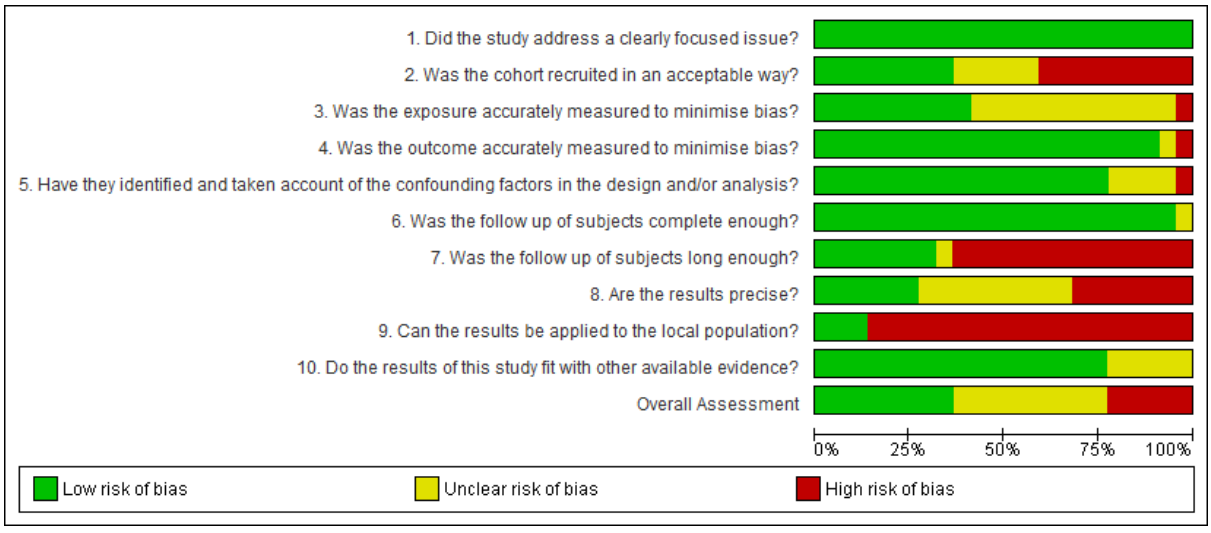
In primary PCI procedures, clinical guidelines generally recommend a DTB time (that is, the time from arrival at the hospital to PCI balloon inflation) of 90 minutes or less, in order to maximise patient outcomes.[312] Two American studies, one large study at low risk of bias[294] and a medium-sized study at unclear risk of bias,[295] reported that low-volume hospitals were significantly less likely to achieve a DTB time of 90 minutes or less than their high-volume counterparts. Kontos et al. reported a relative risk of 0.93 (95% CI: 0.89-0.96) for low-volume hospitals to achieve a DTB time of 90 minutes or less, compared with high-volume centres.[294] Similarly, Kumbhani et al. reported that the odds of low-volume hospitals achieving this DTB goal was 28% less than in high-volume hospitals (OR: 0.72, 95% CI: 0.54-0.96).[295]

In the US Appropriate Use Criteria have been developed for clinical scenarios in which coronary revascularisation may be used to promote the rational use of the procedure in the delivery of high quality care.[313] Using these criteria, one recent study found that higher volume hospitals (>400 total PCI procedures per year) and operators (>200 total PCI procedures per year) tended to perform a higher proportion of inappropriate PCI procedures than their lower volume counterparts.[297] In this study, which was judged to be at low risk of bias, the PCI appropriateness criteria[313] were only applied to a 20% sample, hence this relationship may not exist in the overall study population. However, another study by Fanaroff et al. found similar PCI appropriateness rates for high-, intermediate- and low-volume operators.[292] Furthermore, another study by Fanaroff et al. found that high-volume operators (>100 PCIs per year) conducted a greater proportion of appropriate PCI procedures compared with their lower volume counterparts (<50 PCIs per year) (80.1% vs. 77.6%, p<0.0001).[293] As only three studies in this systematic review investigated this relationship, caution is required when interpreting this finding.

4.3.5 Methodological quality of included studies

Using the CASP quality appraisal tool,[314]eight studies were judged to have an overall low risk of bias,[271, 292, 294, 296, 297, 302, 303, 307] nine were judged to have an unclear risk of bias[289, 290, 293, 295, 298, 299, 301, 305, 308] and five were judged to have a high risk of bias (Figure 4.17).[288, 291, 300, 304, 306]

Figure 4.17: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Most studies were considered at low risk of bias in the following domains (Figure 4.18):

- addressing a clearly focused issue (for example, clear aims/objectives)[271, 288-308]
- accurate measurement of outcome (for example, mortality outcomes retrieved in a consistent manner)[271, 288-303, 305, 307, 308]
- appropriately dealing with confounding factors (for example, multivariate logistic regression models adjusted for important covariates)[271, 288, 290-296, 298-304, 308]
- completeness of follow-up (for example, minimal loss to follow-up)[271, 288-303, 305-308]
- goodness-of-fit of results with other available evidence (for example, results do not completely contradict other studies).[271, 289, 290, 292-294, 296, 297, 299-307]

However, the following domains were considered at high or unclear risk of bias in the majority of studies:

- recruitment of cohort (for example, exclusion of patients older than 65)[291]
- measurement of exposure (for example, reporting caseload over multiple years)[302, 306]
- length of follow-up (for example, in-hospital mortality only)[288-290, 292, 294-296, 298-302, 305, 308]
- imprecision of results (for example, very wide confidence intervals)[295]
- applicability of results to the local population (for example, US studies are not necessarily applicable to the Irish setting).[288-297]

Figure 4.18: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

4.3.6 Certainty of the evidence

The overall certainty of the evidence was assessed and a summary of findings table was created using GRADEpro software[286] for the primary outcome of mortality, as it related to total PCI hospital volume, total PCI operator volume, primary PCI hospital volume and primary PCI operator volume. Evidence from meta-analyses was used to complete the assessment for the first three outcomes, while a narrative synthesis was used to complete the assessment for the latter outcome.

Overall, the certainty of the evidence is 'very low' owing to the observational nature of included studies, a high or unclear risk of bias across many included studies, considerable levels of heterogeneity and some concerns regarding the imprecision of results (Table 4.5).

Table 4.5: Summary of findings table for primary outcomes regarding the relationship between PCI procedural volume and postoperative (in-hospital or 30-day) mortality

Relationship between hospital/operator procedural volume and postoperative (in-hospital/30-day) mortality

Patient or population: Adults (18 years or older) requiring PCI (primary or elective) for cardiac conditions

Setting: Hospital

Intervention: Highest volume hospital/operator

Comparison: Lowest volume hospital/operator

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Mortality in total PCI at hospital level	(9 observational studies)	⨁◯◯◯ VERY LOW [a,b]	**OR 0.84** (0.69 to 1.03)
Mortality in total PCI at operator level	(6 observational studies)	⨁◯◯◯ VERY LOW [c,d]	**OR 0.77** (0.63 to 0.94)
Mortality in primary PCI at hospital level	(7 observational studies)	⨁◯◯◯ VERY LOW [e,f]	**OR 0.77** (0.62 to 0.94)
Mortality in primary PCI at operator level	(2 observational studies)	⨁◯◯◯ VERY LOW [g,h]	N/A

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Of the 9 studies, 3 were low risk of bias, 5 were unclear risk of bias and 1 was high risk of bias
b. I^2 = 86% hence there is substantial heterogeneity
c. Of the 6 studies, 4 were low risk of bias and 2 were unclear risk
d. I^2 = 93% hence there is considerable heterogeneity
e. Of the 7 studies, 3 were low risk, 3 were unclear risk and 1 was high risk of bias
f. I^2 = 78% hence there is substantial heterogeneity
g. Only 2 studies and both had conflicting results
h. Wide confidence intervals for both studies

4.4 Discussion

This systematic review and meta-analysis of contemporary research (studies published since 2008) suggests that a significant inverse relationship persists between total PCI operator volume and postoperative mortality, as well as between primary PCI hospital volume and postoperative mortality, though the evidence is of very low certainty. Furthermore, there is some evidence that high-volume hospitals offer other benefits in terms of association with reduced length of stay and a greater likelihood of achieving target DTB times. No significant association was found between total PCI hospital volume and postoperative mortality, with an apparent temporal trend observed from significant to non-significant pooled effect estimates.

Due to the huge variability in how studies defined low and high volume and differences in how they analysed the data, it is not possible to determine with any degree of certainty, a threshold above which the volume-outcome relationship becomes non-significant. There are also concerns regarding how low and high volume groups were determined, whether they were pre-specified or data driven, and the number of groupings used, as these choices may have introduced bias into the studies. Careful inspection of the forest plots, exploratory meta-regression and examination of the patterns of significance did not reveal a minimum volume threshold. Previous systematic reviews also reported an inability to recommend a specific threshold value for similar reasons.[8-10]

Due to the considerable levels of study heterogeneity, variation in how high and low volume was defined, and some concerns regarding the risk of bias in included studies, these findings must be interpreted with caution. Furthermore, there are limited data to draw any definitive conclusions regarding a specific threshold value; the relationship between primary PCI operator volume and mortality; or whether procedural volume has any meaningful or consistent impact on other clinical outcomes such as MACE, bleeding or unplanned revascularisation. There is evidence to suggest that most, if not all, of the benefits conferred by high-volume operators are attenuated after 30 days. Finally, one recent study that applied US Appropriate Use Criteria found evidence to suggest that higher volume hospitals and operators tend to perform a higher percentage of inappropriate PCI procedures than their lower volume counterparts. Despite these caveats, a volume-outcome relationship still appears to exist and although a specific threshold value cannot be determined, it would appear important that low volume hospitals and operators be kept to a minimum, particularly for primary PCI procedures. While this volume-outcome relationship may exist under certain circumstances, it would appear that volume should not be the only standard used to define an acceptable PCI service.

The findings of this systematic review are different to all three key previous

systematic reviews evaluating the association between PCI volume and postoperative mortality.[8-10] Post et al. conducted a systematic review and meta-analysis investigating the volume-outcome relationship for all PCI procedures, exclusively at the hospital level.[9] The authors found 10 relevant studies (eight of which were conducted in the US), published between 1997 and 2008, based on PCI data from 1984 to 2005.[9] The authors calculated a pooled effect estimate with an OR of 0.87 (95% CI: 0.83-0.91) in favour of high-volume hospitals, with an I^2 value of 38%. However, a notable data extraction error occurred in this systematic review with the inversed values incorrectly entered into the meta-analysis model, resulting in an incorrect value for the pooled effect estimate and uncertainty around the I^2 value.[301] A more recent systematic review and meta-analysis conducted by Lin et al. evaluating the volume-outcome relationship at the hospital level included studies published between 2006 and 2014 and based on PCI data from 1996 to 2009.[8] The authors retrieved 12 studies, six of which were conducted in the US. Similarly, the authors of this study calculated a pooled effect estimate which was significantly in favour of high-volume hospitals (OR: 0.79, 95% CI: 0.72-0.86), with an I^2 value of 38%.

Our finding of a non-significant volume-outcome relationship for total hospital PCI volume therefore contrasts with the findings of earlier systematic reviews.[8, 9] These reviews differ in the included data with our review limited to studies published since 2008 (PCI data from 2000 to 2016). Moreover, we observed an apparent temporal trend, such that a previous statistically significant inverse relationship disappeared with inclusion of additional more recent studies. Notably, the level of heterogeneity between studies has increased substantially, with a higher degree of uncertainty around the true effect estimate found in our systematic review. Our systematic review indicates that a significant volume-outcome relationship may exist at the hospital-level for primary PCI procedures. This relationship has not specifically been evaluated in any previous systematic review.

The third systematic review and meta-analysis conducted by Strom et al. investigated the volume-outcome relationship at the operator level.[10] The authors included studies published between 1997 and 2009, based on PCI data from 1990 to 2005.[10] The authors retrieved 23 studies, 13 of which evaluated mortality as an outcome and eight evaluated MACE as an outcome. The pooled effect estimate however showed no significant relationship between operator volume and mortality (OR: 0.96, 95% CI: 0.86-1.08, with an I^2 value of 61%). The authors did however find a significant relationship between operator volume and MACE (OR: 0.62, 95% CI: 0.40-0.97 with an I^2 value of 97%). This non-significant finding for mortality by the authors, as well as a significant finding for MACE, contradicts our finding of a significant relationship between operator volume and postoperative mortality (OR: 0.77, 95% CI: 0.63-0.94), and our narrative synthesis suggesting no association between operator volume and

MACE. However, some data extraction errors were noted in the meta-analysis model for Strom et al. for at least two of the included studies,[296] hence caution is required when interpreting the calculated pooled effect estimate.

To our knowledge, this is the first systematic review and meta-analysis to evaluate both the hospital and operator volume relationship with mortality, and to analyse these separately for patients undergoing primary PCI in addition to PCI for any indication (total PCI). Previous systematic reviews have combined total and primary PCI populations in their meta-analysis model, which may have introduced bias into the overall findings due to the inherently higher risk of mortality in the latter population.[8-10]

The main strength of this study was the comprehensive search, in-depth analysis and confirmatory methods such as meta-regression, adopted by a team of reviewers experienced in the conduct of systematic reviews and meta-analyses. Furthermore, the assistance of a steering group with contextual knowledge and strong experience of performing and managing PCI added important clinical insights to this review.

One of the main limitations of this study was the evidence of a considerable level of heterogeneity in the quality and design of studies. Meta-regression, subgroup analyses and sensitivity analyses were conducted to try and explain the cause of this heterogeneity. With the exception of median study period (reduction in heterogeneity when an outlier study was removed),[299] no definitive cause could be determined. This may have been due to the limited number of studies included in the meta-regression, illustrating the exploratory nature of this analysis. Although the Cochrane handbook recommends a minimum of ten studies to conduct a meta-regression,[283] other commentators in the field have argued the case for a minimum of four studies for categorical subgroup covariates and six to ten studies for a continuous study-level covariate, particularly where study populations are moderate or large. However these commentators stipulate that in these cases where the number of studies is small, then researchers should only consider one covariate at a time.[315] Nevertheless, we treated the analysis as exploratory and urge caution in its interpretation due to the limited number of included studies.

It is likely that a combination of factors contributed to this heterogeneity, as suggested by these analyses including the number of groupings within studies, the risk of bias, the mean PCI volume of lowest-volume grouping, the lowest-volume threshold and the study period. The considerable levels of heterogeneity observed within these meta-analyses means that the calculated pooled effect estimates must be viewed with caution. Furthermore, although every effort was made to prevent double counting (by stratifying the meta-analysis models according to hospital/operator intervention and primary/total PCI population, and by only

including one study from each data source), it is possible that some US patients may have been captured in more than one data source (for example, the New York State Registry, the National Inpatient Sample, the CathPCI Registry, the Veterans Affairs database and the Get With the Guidelines Registry). However, as individual patient data were not available, it was not possible to ascertain whether any overlap existed, and therefore an assumption was made by the research team that there was negligible overlap between studies.

There are several key inherent issues with the design and conduct of the included studies which limits our ability to draw robust conclusions on certain issues. A key issue was the inconsistent manner in how the data were reported, which prevented us from being able to analyse the threshold effect with any degree of certainty. Importantly, the findings for any one of the studies are highly dependent on the spread of volumes within that study, so findings may not be widely generalisable. Furthermore, the manner in which some of the study data were divided (for example, into deciles)[299] makes it likely that the extremes of volumes were being compared. These may not be nationally representative, and it is possible that case mix adjustment did not control for all the potential confounders. Another issue related to the difficulty demonstrating a statistically significant relationship at the operator level given that a) poor outcomes are quite rare and b) the annual number of cases per operator is relatively small. Furthermore, some studies did not adjust for operators conducting procedures in multiple locations.[296, 297, 299, 306] With regards to the secondary outcomes, the substantial heterogeneity in the definitions and composites used across included studies makes it difficult to fully interpret the findings. Furthermore, there were limited data to examine the volume-outcome relationship in more complex procedures and subpopulations, such as unprotected LMPCI or MVPCI.

It is noted that all included studies were observational in nature. Randomised controlled trials to investigate any potential causal relationship between volume and mortality would be impractical and possibly unethical in this type of situation. Although all included studies were risk-adjusted for certain confounders, it is likely given the observational designs that other important confounders were not considered. For example, only one study evaluated the impact of time-to-presentation on the volume-outcome relationship and found it to have a significantly important interaction on this relationship.[305] Furthermore, no study controlled for the actual distance travelled by each patient to the treating PCI centre. This information would be most helpful for service provision going forward; if regionalisation of primary PCI centres results in the closure or downgrading of smaller regional centres, patients would need to travel further to get the appropriate care. Commentators in the field have acknowledged that although volume is an important metric, it should not be considered the only indicator of quality.[13, 275, 278] Moreover, the availability of on-site surgical backup is a

potentially important influence on mortality outcomes,[316] and was only adjusted for in one study.[295] This could be an important confounder, with the potential that the volume-outcome relationship is influenced by the hospital-level resources rather than the number of procedures undertaken.

An important observation was that a disproportionately higher number of emergent or STEMI procedures tended to be conducted by low-volume hospitals and operators.[288, 290, 292, 293, 298, 308] This finding may indicate the important role these low-volume hospitals and operators may have in terms of serving sparsely populated regions.

Another observation reported in a recent study was an apparent relationship between procedural volume and the proportion of inappropriate PCI (as defined use US Appropriate Use Criteria) undertaken, with higher levels of potentially inappropriate PCI undertaken by high volume hospitals and operators.[297] The study authors noted that since the publication of the Appropriate Use Criteria in 2009, there have been significant reductions in volume of non-acute PC with a decline in the proportion of non-acute PCIs classified as inappropriate. However they also noted that hospital-level variation in inappropriate PCI persists.[297] Due to the use of arbitrary minimum volume thresholds by certain guidelines, service funders and regulatory bodies, it has been argued that this may motivate some operators and hospitals to perform PCI in some patients who have a lower capacity to benefit from the procedure, in order to meet minimum volume requirements.[13]

A key finding of our study was the apparent temporal trend from significant to non-significant pooled effects estimates observed for total PCI hospital volume. With advances in interventional cardiology in terms of increasingly sophisticated operating techniques, more effective drug-eluting stents and improvements in medical management it is likely that some of these factors may have mitigated the importance of volume on mortality.[13] Furthermore, introduction of advanced systems of care, streamlined processes and governance structures may also have improved standards across the board.[11] However due to the implementation of minimum volume standards, it is possible that the observed decrease in proportion of low-volume hospitals and operators over time may also have moderated this volume-outcome relationship. What constitutes 'low-volume' appears to have changed over time, and the use of traditional cut-points may no longer be sensitive enough to detect any significant difference, particularly for a relatively rare outcome such as mortality. Therefore the reason for this temporal trend is unclear.

Although no significant temporal changes were observed in either of the other two meta-analyses, meta-regression of total PCI operator volume suggests that median study period may account for 60% of the between-study differences. Particularly as the operator-level studies tended to be more recent than the hospital-level studies

(range of publication years = 2014-2019 vs. 2008-2019), there is a possibility of a time lag effect; hence it is possible that in the future this operator volume-outcome relationship may attenuate also. However, no temporal change was apparent for primary PCI hospital volume. Sensitivity analyses conducted for this outcome suggests that there is robustness around this particular pooled effect estimate. This is potentially reflective of the life-threatening nature of STEMIs, and the need for a certain level of competence and systems of care. Therefore the influence of hospital volume may be particularly important for primary PCI.

We limited inclusion to studies published since 2008 due to significant recent advances in PCI techniques and post-operative medical management.[12] By focusing on more recent data, our pooled effect estimate is possibly more reflective of current practice than that calculated by any of the previous systematic reviews.[8-10] [317] It is possible that the quality gap between high and low volume is narrowing, and standards may be improving across the board.[278, 303] Furthermore, several authors found that very few operators or hospitals could be classified as low volume according to traditional definitions.[271, 292, 293, 303] For example, O'Neill et al. reported that only 0.6% of all PCI procedures in England and Wales were conducted in low-volume hospitals (199 or fewer annual procedures) between 2007 and 2013, and found no association between volume and outcome.[303] Yet the authors of this study did not argue against the promotion of minimum volume thresholds, but rather suggested that the findings highlight how regionalisation efforts across the UK may have resulted in a uniformly high standard of care.[303] Similar to Ireland, the volume of procedures within centres tends to be increasing, suggesting that traditional definitions of low volume may no longer be relevant.

From this systematic review, several gaps for future research were apparent. Firstly, if volume was reported as a continuous outcome, this would enable future volume-outcome studies to undertake more appropriate comparisons rather than based on arbitrary cut-off values. Secondly, more volume-outcome studies with longer follow-up periods should be conducted to allow for meta-analyses of long-term outcomes. Thirdly, more research is required to examine the link between the establishment of minimum volume thresholds and the performance of inappropriate PCI in order to fully understand and manage any unintentional negative consequences. Finally, more studies should be conducted specifically examining the relationship between primary PCI operator volume and mortality outcomes, as only two studies to date have investigated this critical relationship.[271, 296]

In conclusion, this systematic review and meta-analysis suggests that a volume-outcome relationship may still exist in favour of high-volume operators and high-volume primary PCI hospitals, however no significant association was found between total PCI hospital volume and mortality. A temporal trend was observed indicating

that the volume-outcome relationship may be attenuating over time. Due to the considerable levels of heterogeneity, concerns regarding the risk of bias of included studies and variations with how high and low volume were defined, these results must be viewed with caution. Furthermore, it is not possible to determine with any degree of certainty a specific minimum-volume threshold. While a volume-outcome relationship may exist under certain circumstances, volume should not be the only standard used to define an acceptable PCI service.

4.5 Key points

- A systematic review and meta-analysis was undertaken to examine the relationship between PCI procedural volume and patient outcomes, in light of advances in interventional cardiology.
- Of 1,154 unique records retrieved, 22 studies conducted in eight countries were included. The 22 studies included a total of 6,432,265 patients or procedures.
- All included studies were observational in nature – 17 were cross-sectional studies and five were cohort studies.
- Overall, the certainty of the evidence is 'very low' owing to the observational nature of included studies, a high or unclear risk of bias across many included studies, the considerable levels of heterogeneity and some concerns regarding the imprecision of results.
- No significant association was found between total PCI hospital volume and mortality (odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.69-1.03). The certainty of evidence was graded as 'very low' due to considerable levels of heterogeneity (I^2 = 86%) and high/unclear risk of bias in included studies. A temporal trend towards a non-significant relationship was observed, however the reason for this is unclear.
- The pooled effect estimate was found to be significantly in favour of high-volume operators, for total PCI procedures (OR: 0.77, 95% CI: 0.63-0.94) though this was graded as 'very low' certainty evidence due to the considerable levels of heterogeneity (I^2 = 93%) and high/unclear risk of bias in included studies.
- The pooled effect estimate was found to be significantly in favour of high-volume hospitals, for primary PCI procedures (OR: 0.77, 95% CI: 0.62-0.94)

though this was graded as 'very low' certainty evidence due to the considerable levels of heterogeneity (I^2 = 78%) and high/unclear risk of bias in included studies.

- Only two studies investigated the relationship between primary PCI at the operator level and mortality, and these studies reported conflicted findings.
- With regards methodological quality, eight studies were judged to have an overall low risk of bias, nine were judged to have an unclear risk of bias and five were judged to have a high risk of bias.
- Definitions of high and low volume varied widely between studies, and hence it was not possible to calculate a minimum volume threshold.
- In two studies that evaluated long-term mortality outcomes, it would appear that the volume-outcome relationship attenuated over time in these studies.
- The volume-outcome relationship within specific patient subpopulations was inconsistent. The association between procedural volume and PCI complications was also inconsistent.
- There appeared to be a consistently significant relationship between procedural volume and healthcare utilisation or process outcomes, in favour of high-volume operators and hospitals, though caution is required when interpreting this finding due to the limited number of studies examining this relationship.

5 Review question four: pharmacoinvasive strategy versus primary PCI for STEMI

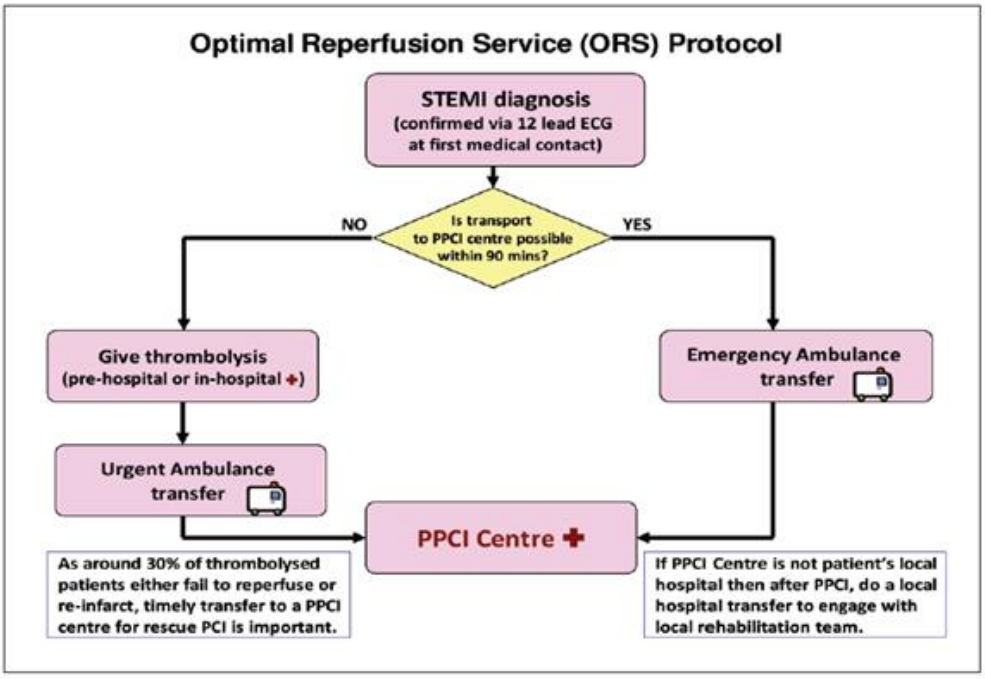
5.1 Introduction

Primary PCI is recommended as the preferred reperfusion strategy for STEMI; however, this is contigent on the procedure being conducted in a timely manner.[212, 234] Evidence suggests that total ischaemic time (that is, time from symptom onset to reperfusion) may be more important in predicting mortality in patients with STEMI than commonly measured metrics such as door-to-balloon time (that is, time from hospital arrival to PCI balloon inflation).[318, 319] Providing PCI for STEMI is a major challenge for many healthcare systems given the need to balance the volume and resource requirements necessary for a primary PCI centre to meet minimum standards and achieve good patient outcomes and the efficient provision of care, particularly in low-population density and geographically remote regions.

An alternative to primary PCI, known as the pharmacoinvasive strategy, involves fibrinolysis combined with timely routine (usually between 3–24 hours later) coronary angiography, with or without PCI. It is recommended when primary PCI cannot be achieved within 120 minutes of STEMI diagnosis and where there are no contraindications to fibrinolytic therapy.[212, 234] If fibrinolysis is determined to have failed, then patients undergo rescue PCI immediately, otherwise coronary intervention is delayed at least two to three hours.[212, 234] This delay between fibrinolytic administration and coronary intervention is important due to the paradoxical early pro-thrombotic effects associated with fibrinolytic agents,[320] which caused the premature termination of a large randomised controlled trial (RCT) because of excess in-hospital mortality in the intervention arm.[321] Therefore, this specific approach known as 'facilitated PCI' (whereby fibrinolytic agents are administered with the intention of performing PCI) is not recommended by guidelines due to its detrimental effects.[212, 234]

Although primary PCI is considered the gold standard of STEMI treatment, the incremental benefit of primary PCI over immediate fibrinolysis is particularly susceptible to treatment delays.[322] The decision whether to proceed with primary PCI or a pharmacoinvasive strategy relates primarily to the estimated transport time from STEMI diagnosis to the nearest PCI-capable centre. The current optimal reperfusion service (ORS) protocol for Ireland recommends that if the transfer time is greater than 90 minutes (allowing for an additional 30 minutes door-to-balloon time once the patient arrives at the hospital), then a pharmacoinvasive approach should be undertaken (Figure 5.1).[175]

Figure 5.1: HSE acute coronary syndrome model of care optimal reperfusion service protocol



Key: ECG – electrocardiogram; HSE – Health Service Executive; ORS – optimal reperfusion service; PPCI – primary percutaneous coronary intervention; STEMI – ST elevation myocardial infarction.

Previous systematic reviews have compared pharmacoinvasive strategies (and other similar fibrinolytic approaches) with primary PCI. While they have reported some conflicting findings, generally all concluded that these pharmacoinvasive approaches may be considered as a suitable alternative to primary PCI if there are delays in providing PCI in a timely manner.[323-325] However, due to significant advances in PCI practices and perioperative management in recent times, it is uncertain whether the balance of harms and benefits has shifted.[8, 57] Furthermore, older trial data upon which a lot of these systematic reviews rely may no longer provide a fair reflection of current STEMI management, particularly as the optimal time for routine coronary angiography (that is 3–24 hours post fibrinolysis) has only been established in recent years. Therefore, it is unclear whether a pharmacoinvasive strategy remains a suitable alternative to primary PCI under both RCT and 'real-world' scenarios. The aim of this systematic review and meta-analysis was, therefore, to examine the safety and effectiveness of a pharmacoinvasive strategy compared with primary PCI for adults diagnosed with STEMI and to quantify any identified harms and benefits in light of advances in interventional cardiology.

5.2 Methods

5.2.1 Review question

What is the safety and effectiveness of a pharmacoinvasive strategy compared with primary PCI for adults diagnosed with STEMI?

The population, intervention, comparator, outcomes and study designs of interest in this review question are described in Table 5.1.

Table 5.1: PICOS for RQ4

Population	Adults (18 years or older) diagnosed with STEMI
Intervention	Pharmacoinvasive strategy comprising: 1. *routine rapid transfer to a PCI-capable centre after fibrinolysis* 2. *immediate PCI **only** for patients with failed fibrinolysis; and* 3. *routine angiography with or without PCI within 24 hours after successful fibrinolysis (usually within 3-24 hours post fibrinolytic administration).* *Excludes facilitated PCI, whereby fibrinolysis is administered with the intent of performing immediate PCI ≤ 2 hours after fibrinolysis administration)*[212]
Comparator	Primary PCI *(defined as percutaneous coronary intervention in the setting of STEMI without previous fibrinolysis)*[12]
Outcomes	▪ Mortality (all-cause and cardiac), ▪ Survival ▪ Major adverse cardiac event / major adverse cardiac and cerebrovascular events (MACE/MACCE) ▪ Recurrent MI / re-infarction ▪ Heart failure ▪ Cardiogenic shock ▪ Stroke (haemorrhagic and ischaemic) ▪ Bleeding (major and minor) ▪ Intra-cranial haemorrhage (ICH), ▪ Healthcare utilisation outcomes ▪ Health-related quality of life
Study design	RCTs and observational studies

5.2.2 Search strategy

Electronic searches were conducted in PubMed, Embase, CINAHL Plus and the

Cochrane Library (which includes the Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) database and the National Health Service Economic Evaluation Database (NHS EED)) for the period 1 January 2008 to 1 August 2019. The search strategy used database-specific search terms (Appendix 1,Table A.4). Clinical trials registries were searched (ClinicalTrials.gov, EU Clinical Trials Register, International Standard Randomised Controlled Trials Number (ISRCTN) Registry and International Clinical Trials Registry Platform (ICTRP)). Grey literature sources were also searched (Appendix 2, Table A.5 and Table A.6), along with the first five pages of Google and Google Scholar. Additional search methods used included forward citation searching of eligible studies, hand searching relevant journals (*Heart*, *European Heart Journal*, *Journal of the American College of Cardiology*, *Canadian Journal of Cardiology*, *Catheterization and Cardiovascular Interventions*) and systematic reviews and searching reference lists of included studies.

5.2.3 Selection criteria

Initial duplicates were removed by one reviewer. Remaining records were independently screened by two reviewers, first by title and abstract and subsequently by full-text. Any disagreements were resolved through discussion, and, where necessary, a third reviewer. All records that were excluded after full-text screening were reported along with the reason for their exclusion (Appendix 6, Table A.25). All RCTs and observational studies comparing a pharmacoinvasive strategy with primary PCI in patients diagnosed with STEMI were included, according to the inclusion and exclusion criteria outlined in Table 5.2.

For the purpose of this study, a pharmacoinvasive strategy was defined as:

> A reperfusion strategy using adjunctive PCI after initial pharmacological reperfusion with fibrinolysis, consisting of:
> 1) routine rapid transfer to PCI centres after fibrinolysis
> 2) immediate PCI only for patients with failed fibrinolysis (defined as <50% resolution of the ST-elevation from the first ECG, or the persistence of typical angina symptoms 90 minutes from the time of fibrinolysis)[323]
> 3) routine angiography with or without PCI within 24 hours after successful fibrinolysis (usually within 3–24 hours post fibrinolytic administration).[212]

For the purpose of this study, a 'facilitated PCI' approach was defined as fibrinolysis administration with the intention of performing immediate PCI ≤ 2 hours after fibrinolysis administration.[212]

Table 5.2: Inclusion and exclusion criteria for RQ4

Inclusion Criteria	Exclusion Criteria
▪ Comparing a pharmacoinvasive strategy with a primary PCI strategy ▪ STEMI patients ▪ Primary data (that is, editorials and reviews are excluded) ▪ Reports at least one of the predefined primary outcomes ▪ RCT or parallel comparative observational studies ▪ For observational studies: reports adjusted rates (odds ratios (ORs), hazard ratios (HRs), relative risks (RRs)), and/or is propensity-matched	▪ 'Facilitated PCI' strategy ▪ Coronary angiography >24 hours post fibrinolysis administration, unless the protocol explicitly aims for <24 hours but this cannot occur in a proportion of patients due to system delays ▪ Fibrinolytic therapy administration without urgent transfer to a PCI-capable centre ▪ Ischemia-guided management after fibrinolysis (i.e. angiography and PCI only in patients with evidence of myocardial ischaemia) ▪ Non ST-elevation ACS patients (for example, NSTEMI, unstable angina) ▪ Multiple observation studies based on the same registry; only the most recent or most informative article will be included ▪ No relevant outcomes reported ▪ Conference papers and abstracts where the full paper is unobtainable ▪ Non-comparative studies ▪ For experimental studies: Historically controlled studies, controlled before-and-after studies, interrupted time series studies and other non-randomised controlled studies ▪ Paper published prior to 2008 (Studies relating to interventions published prior to 2008 (such as long-term follow up studies) will be excluded. ▪ Paediatric (<18 years old) population

Only studies published since 2008 were included due to significant advances in interventional cardiology and peri-operative management in recent years. Studies relating to interventions published prior to 2008 (such as long-term follow-up studies) were not included.

Both RCTs and observational studies were included but analysed separately. Patients

for whom fibrinolysis is contraindicated are not eligible for the pharmacoinvasive strategy but can undergo primary PCI. Conversely, certain patients may only have received a pharmacoinvasive strategy due to delays in stabilising the patient or excessive travel distances. Therefore, there is a potential for significant bias due to confounding and baseline differences in the two intervention arms. Hence, observational studies must have reported adjusted outcomes and or be propensity matched in order to be included.

To be included, studies must have reported a comparison of a pharmacoinvasive strategy (but not a 'facilitated PCI' strategy) with a primary PCI strategy in STEMI patients. This is in line with the current model of care provided in Ireland for patients diagnosed with STEMI (Figure 5.1).

5.2.4 Data extraction and management

The results of the search were exported to Covidence systematic review software, which was used to manage citations and perform title and abstract screening. Duplicates were identified and removed. A flow diagram using PRISMA guidelines was generated to report the selection process and all results (

Figure 5.2). Data were extracted for all included studies. Study authors were contacted for additional information if required. Data extraction was performed independently by a minimum of two people with any disagreements being resolved by discussion, and, where necessary, a third reviewer. The data extraction tool was piloted on two studies initially. For this review question, Covidence was also used for data extraction and management purposes.

The following data were extracted from each included study:

- year of publication
- country
- study period
- study design
- number of patients in each group
- patient demographics (age, % men, % hypertension, % smokers, % diabetes mellitus, % cardiogenic shock, % prior heart failure, % prior stroke, % prior MI)
- adjunctive treatment characteristics (% stent, % and type of glycoprotein IIb/IIIa) inhibitors
- inclusion and exclusion criteria
- fibrinolytic agent and dose used
- intervention and control strategy
- primary endpoint
- symptom onset to needle/balloon time
- needle-to-balloon time
- % undergoing rescue PCI
- database (if registry-based observational study)
- data type (for example, administrative/clinical, if observational study)
- risk adjustment covariates (if observational study)
- process measures (for example, distance to hospital, time to treatment, out of hospital cardiac arrest, radial artery access and use of drug-eluting stents)
- hospital characteristics (for example, presence of on-site surgical cover)
- severity of disease (for example, cardiogenic shock)
- treatment differences (for example, rescue PCI).

The primary effectiveness outcomes were:

- mortality (all-cause and cardiac)
- survival
- re-infarction
- heart failure
- cardiogenic shock.

The primary safety outcomes were:

- bleeding (major, minor and total bleeding)
- intra-cranial haemorrhage (ICH)
- stroke (ischaemic and total strokes)
- anaphylaxis/other drug adverse event.

The secondary outcomes were:

- healthcare utilisation outcomes
- health-related quality of life.

Composite outcomes were analysed separately due to inconsistency between studies in the endpoints that were combined.

5.2.5 Risk of bias and quality appraisal

Risk of bias assessment and quality appraisal of the included studies were conducted independently by two reviewers. Any disagreements were resolved by consensus or arbitration by a third reviewer if necessary. RCTs underwent risk of bias assessment using the Cochrane risk of bias tool version two (RoB 2.0).[326] Observational studies underwent quality appraisal using a modified version of the Critical Appraisal Skills Programme (CASP) tool for cohort studies.[279] According to the developers of the RoB 2.0, assessments should be made at the outcome-level rather than at the study-level.[326] Hence, for consistency, two of the main outcomes (all-cause mortality and bleeding) were selected to undergo both RoB 2.0 and CASP appraisal. Both tools were piloted by two reviewers initially, and any clarifications were made as necessary.

5.2.6 Data synthesis

The guideline for evaluating the clinical effectiveness of health technologies in Ireland was adhered to with regard to data synthesis.[280] Meta-analyses were conducted using RevMan version 5.3 or R version 3.5.2 (2018) where there were a minimum of four studies for any of the pre-specified outcomes in Section 5.2.4. Specific statistical methods were required for several meta-analyses with zero events.[327] For the synthesis of these zero event studies, Bayesian meta-analyses using beta-normal hierarchical models were conducted in statistical software R version 3.5.2 (2018) using the MetaStan programme. The most appropriate effect estimates are presented in the main text, taking into consideration the rarity of events. Publication bias was not formally assessed as the minimum requirement of 10 studies to conduct this test was not met in any single meta-analysis; however, funnel plots were visually inspected. A narrative synthesis was undertaken for the findings not included in the meta-analysis. In studies that presented findings in

graph form only, the effect estimates and 95% confidence intervals were extracted from the graphs using the online resource WebPlotDigitizer (automeris.io/WebPlotDigitizer) for inclusion in the meta-analyses. Data from RCT and observational studies were pooled separately and not combined.

5.2.6.1 Synthesis of RCTs

For RCTs, the total numbers of outcome events in each arm along with the total number of patients randomised to each arm were exported into RevMan and R version 3.5.2 (2018). Some of the analyses presented here used methods specific to rare outcomes and sparse data. For those methods, from a statistical perspective, the odds ratio is preferred to the risk ratio. For consistency, all analyses in this section are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Outcomes from individual studies were combined using random effects Mantel–Haenszel models (using the Sidik-Jonkman estimator for tau^2, meta package and metabin command in R). For outcomes with zero events a beta-normal hierarchical model (Metastan package in R) was used.

Pooled effect estimates were calculated with primary PCI outcomes as the reference (control) group due to its acceptance as the gold standard treatment for STEMI.[12, 212] The MetaStan programme in R generates overall pooled effect estimates, but does not generate forest plots; hence, forest plots were generated through RevMan (with the pooled effect estimate suppressed) for visual purposes only.

For any outcome found to have a significant treatment effect, the number needed to treat for an additional harmful/beneficial outcome (NNTH/NNTB) with the pharmacoinvasive strategy compared with primary PCI to prevent or cause one event was estimated, using the following equation[328]:

$$NNTH/NNTB = \frac{1}{|(BR - \frac{OR * BR}{1 - BR + OR * BR})|}$$

Key: NNTH — number needed to treat for an additional harmful outcome; NNTB - number needed to treat for an additional beneficial outcome; BR — baseline risk; OR – odds ratio.

This equation was also used to generate the 95% CIs around the NNTH/NNTH estimate. Of note, this equation does not take into account any uncertainty around the baseline risk measurement.

Sensitivity analyses were conducted to assess the impact on the overall pooled effect estimate of:

- using alternative models (that is, using a beta-binomial model, beta-normal

hierarchical model, peto odds ratio model, random-effects model)
- a study-by-study exclusion process.

Subgroup analyses were conducted to assess the impact on the overall pooled effect estimate of:

- different median/mean symptom onset-to-balloon times for primary PCI (≤ 3 hours vs. > 3 hours)
- different median/mean symptom onset-to-needle times for the pharmacoinvasive strategy (≤ 2 hours vs. > 2 hours)
- risk of bias
- use of fibrin-specific (alteplase, reteplase, tenecteplase and lanoteplase) vs. non-fibrin-specific (streptokinase, urokinase, anistreplase) fibinlolytic agent
- use of full-dose vs. half-dose fibrinolytic regimens
- diagnosis of STEMI within vs. outside of PCI-capable centres.

5.2.6.2 Synthesis of observational studies

For observational studies, the adjusted outcomes of the pharmacoinvasive group compared with the primary PCI group (reference) from each study were exported to RevMan 5.3. If the pharmacoinvasive group was used as the reference, the results were transformed (1/effect size) to fit the statistical model. Results were presented as ORs with 95% CIs. Outcomes from individual studies were combined using random-effects inverse-variance models. As no single adjusted outcome was reported by at least four observational studies, pooling of effect estimates was not possible. However, the forest plots are presented below without pooled effect estimates for visual purposes and the results are narratively synthesised and discussed in conjunction with the corresponding findings from the synthesis of RCTs.

5.2.7 Assessing the certainity of the body of evidence using the GRADE approach

The overall certainty of the evidence was assessed, and a summary of findings table created using GRADEpro software for the primary outcomes.[286] This was done separately for evidence from RCTs and observational studies. The evidence was examined independently by two reviewers, with any discrepancies decided by consensus.

5.2.8 Protocol deviations

Protocol deviations are listed in Appendix 10.

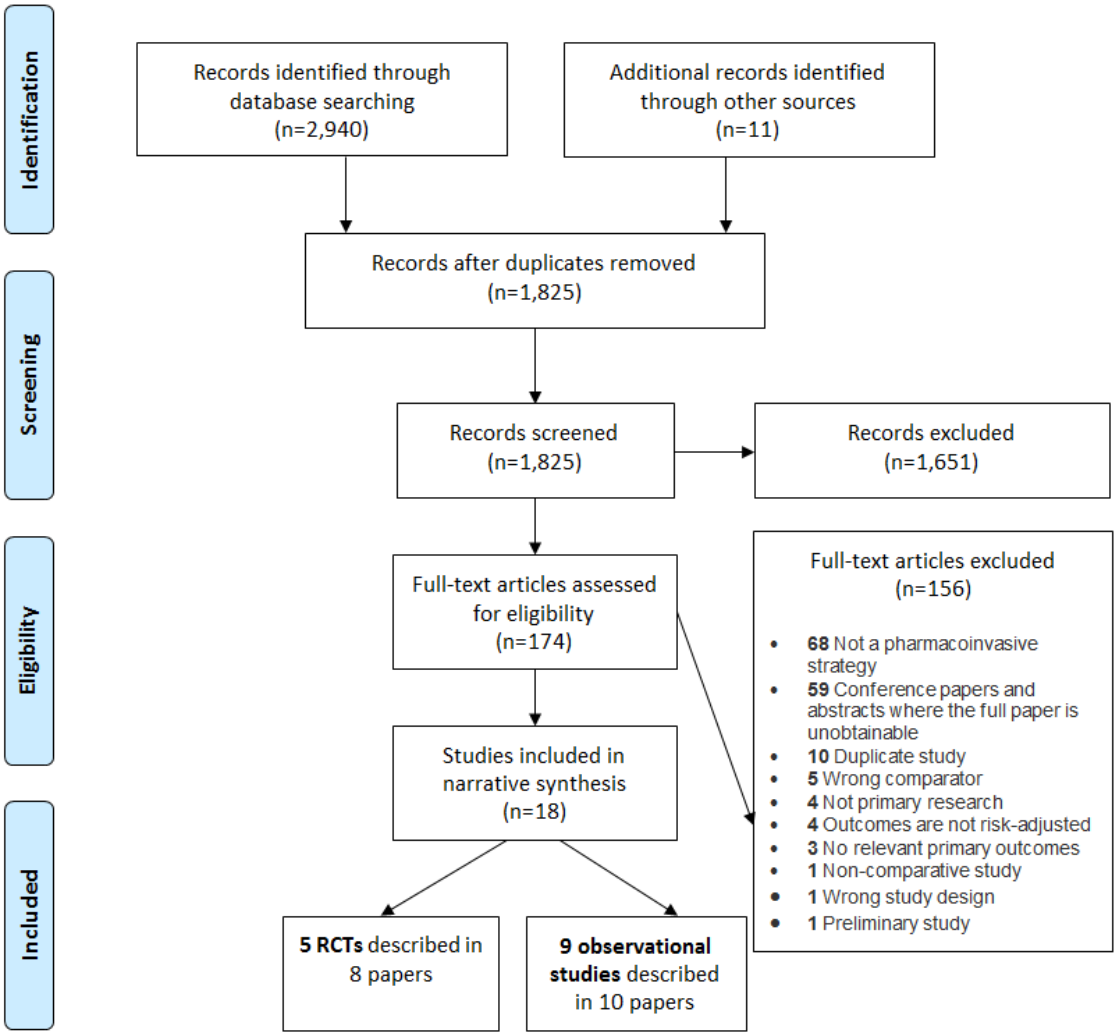
5.3 Results

5.3.1 Search results

The search of electronic databases identified 2,940 potentially relevant records; 11 potential records were identified through searches of the grey literature and other sources. After the exclusion of duplicates, 1,825 records were screened independently by two reviewers, with a further 1,651 records excluded based on titles and abstracts. A total of 174 full-text articles were assessed for eligibility. Of these, 156 records were excluded (Appendix 6, Table A.25) according to the inclusion and exclusion criteria (Table 5.2). This resulted in 18 papers being included in the review (

Figure 5.2). Of these 18 papers, eight described five unique RCT studies and 10 described nine unique observational studies. Therefore, a total of 14 unique studies were included — five RCTs and nine observational cohort studies.

Figure 5.2: PRISMA flow chart of included studies for RQ4



5.3.2 Characteristics of included studies

A summary of study characteristics is provided below in Table 5.3, with more in-depth detail provided in Appendix 3 (Table A.11).

Table 5.3: Table of characteristics of included studies for RQ4

Author or Trial name and Year of publication, Country, Total population, Study period.	Number (%) in groups	Age	Men n(%)	Fibrinolytic agent used in PI group	No.(%) Killip class I	HT n(%)	DL n(%)	FH of CVD n%	DM n(%)	Prior MI n(%)	Smoking current/ recent	No. of rescue PCI in PI group n(%)	Time-to-treatment	Outcomes reported
Randomised Controlled Trials (n=5)														
EARLY-MYO 2019[329] *China* N=344 Study period *2014 – 2016*	PI 171 (49.7) PPCI 173 (50.3)	58 (51–64)	306 (89.0)	Half-dose ALT	322 (93.6)	176 (51.1)	75 (21.8)	27 (7.8)	84 (24.4)	NR	NR	41 (24)	Median SONT/SOBT (IQR) PI 210 (166–270) PPCI 280 (214–340) Median NBT (mins): 485	30 days: ACM, RI, HF, CM, CE, stroke, ICH, IS, TB, MaB, MiB
Vyshlov 2015[330] *Russia* N=326 Study period *NR*	PI 164 (50.3) PPCI 162 (49.7)	57.7± 10.5	228 (70)	Unknown dose TEN or half-dose STR	NR	272 (83.4)	286 (87.7)	NR	65 (19.9)	NR	218 (66.9)	NR	Mean SONT/SOBT ± SD PI 131.7 ± 88.6 PPCI 232 ± 71.6 Median NBT: NR	In hospital: ACM, RI, HF, CE, IS
STREAM study 2013[331-334] *Austria, Belgium, Brazil, Canada, France, Germany, Greece, Italy, Norway, Peru,*	PI 944 (49.9) PPCI 948 (50.1)	59.6 ± 12.4	1490 (78.8)	Full-dose TEN Changed in August 2009 Dose reduced by 50% in those aged ≥ 75 years	1686 (94.2)	848 (45.5)	NR	NR	236 (12.6)	179 (9.5)	NR	331 (36.3)	Median SONT/SOBT (IQR): PI: 100 (75–143) PPCI: 178 (135–230)	30 days: ACM, CS, RI, HF, CM, CE, RH, stroke, ICH, IS, MaB, MiB, RBT, ADE

Author or Trial name and Year of publication, Country, Total population, Study period.	Number (%) in groups	Age	Men n(%)	Fibrinolytic agent used in PI group	No.(%) Killip class I	HT n(%)	DL n(%)	FH of CVD n%	DM n(%)	Prior MI n(%)	Smoking current/ recent	No. of rescue PCI in PI group n(%)	Time-to-treatment	Outcomes reported
Poland, Russia, Serbia, Spain, UK N=1892 Study period *2008 - 2012*													Median NBT (mins): 483	1 year: ACM, CM, SU
Bendary 2018[335] *Egypt* N=60 Study period *2016 – 2017*	PI 30 (50.0) PPCI 30 (50.0)	52.3± 10.1	47 (78.3)	Full-dose STR	NR	18 (30)	7 (11.6)	5 (8.3)	19 (31.6)	NR	41 (68.3)	NR	Mean SONT/SOBT ± SD PI 110± 27.5 PPCI 186.8± 16.6 Mean ± SD NBT (hours): 14.2 ±6.8	In hospital: ACM, RI, HF, stroke, MaB 30 days: ACM, RI, CE, RH, stroke, MaB
GRACIA-4 2017[336] *Spain* N=355 Study period *2010 - 2014*	PI 177 (49.9) PPCI 178 (50.1)	61.9 ± 12.7	288 (81.1)	Full-dose TEN	321 (92.5)	156 (43.9)	153 (43.1)	NR	61 (17.2)	30 (8.5)	166 (46.7)	71 (40.1)	Median SONT/SOBT (IQR) PI 170 (117.50-240) PPCI 225 (160-315) Median NBT (mins): 430	30 days: ACM, RI, CM, CE, RH, stroke, ICH, TIA, IS, TB, MaB, MiB, RBT 1 year: ACM, RI, CM, CE, RH, stroke, ICH, TIA, IS, TB, MaB, MiB, RBT
Observational Cohort Studies (n=9)														
Bessonov 2016[337]	PI 144	59.1 ±11.1	541 (75)	Full-dose TEN	605 (90.7)	574 (79.6)	679 (94.2)	NR	119 (16.5)	120 (16.6)	NR	NR	Median SONT/SOBT	In hospital: ACM, RI, CE,

Author or Trial name and Year of publication, Country, Total population, Study period.	Number (%) in groups	Age	Men n(%)	Fibrinolytic agent used in PI group	No.(%) Killip class I	HT n(%)	DL n(%)	FH of CVD n%	DM n(%)	Prior MI n(%)	Smoking current/ recent	No. of rescue PCI in PI group n(%)	Time-to-treatment	Outcomes reported
Russia N=721 Study period *2008 – 2013*	(20.0) PPCI 577 (80.0)												(IQR) PI 80 (55-172) PPCI NR Median NBT (mins): 270 (120-540)	TB,
Siontis 2016[156] *US* N=1701 Study period *2004 – 2012*	PI 364 (21.4) PPCI 1337 (78.6)	64.0 ± 13.8	1220 (71.7)	Full-dose RET or TEN	NR	1068 (62.8)	1064 (62.6)	NR	301 (17.7)	291 (17.1)	1100 (64.7)	153 (42)	Median SONT/SOBT (IQR) PI NR PPCI NR Median NBT (mins): NR	In hospital: ACM, ICH 30 days: ACM 5 years: ACM, SU
Victor 2014[338, 339] *India* N=200 Study period *2011 - 2013*	PI 45 (22.5) PPCI 155 (77.5)	54	173 (86.5)	Full-dose TEN	130 (65.0)	61 (30.5)	12 (6)	22 (11)	102 (51)	NR	47 (23.5)	4 (12.1)	Median SONT/SOBT (IQR) PI 245 (185-395) PPCI 260 (185-390) Median (IQR) NBT (hours): 12.25 (4.5-23.67)	In hospital: ACM, CE 30 days: ACM, CE, ICH, TB, MaB, MiB 1 year: ACM, CE 3 months: ACM, CE 6 months: ACM, CE 2 years: ACM,

Author or Trial name and Year of publication, Country, Total population, Study period.	Number (%) in groups	Age	Men n(%)	Fibrinolytic agent used in PI group	No.(%) Killip class I	HT n(%)	DL n(%)	FH of CVD n%	DM n(%)	Prior MI n(%)	Smoking current/ recent	No. of rescue PCI in PI group n(%)	Time-to-treatment	Outcomes reported
														CE
Sierra-Fragoso 2018[340] *Mexico* N=400 Study period *2016 - 2017*	PI 137 (34.2) PPCI 263 (65.8)	NR	310 (77.5)	NR	358 (89.5)	224 (56.0)	112 (28.0)	NR	187 (46.8)	NR	228 (57.0)	35 (30.7)	Mean SONT/SOBT ± SD PI NR PPCI 309 ± 189 Mean ± SD NBT (hours): NR	In hospital: ACM, RI, CE, stroke, TB, MaB,
Shavadia 2013[341] *Canada* N=3013 Study period *2006 - 2011*	PI 1504 (49.9) PPCI 1509 (50.1)	NR	NR	Full-dose TEN	NR	NR	NR	NR	NR	NR	NR	348 (23.1)	Mean SONT/SOBT ± SD PI NR PPCI NR Mean ± SD NBT (hours): NR	In hospital: ACM, CS, RI, HF, CE, ICH, TIA, IS,
Kumbhani 2019[342] *India* N=1215 Study period *2012 – 2014*	PI 400 (32.9) PPCI 815 (67.1)	54.3 ± 11.7	1045 (86)	Unknown dose STR	NR	314 (25.8)	NR	NR	350 (28.8)	NR	441 (36.3)	NR	Mean SONT/SOBT ± SD PI NR PPCI NR Mean ± SD NBT (hours): 18.4 ± 32.3	In hospital: ACM, MaB 1 year: ACM 2 year: ACM
Rashid	PI	62.4 ±	886	Full-dose TEN	1098	576	517	NR	207	168	519	NR	Median	In hospital:

Author or Trial name and Year of publication, Country, Total population, Study period.	Number (%) in groups	Age	Men n(%)	Fibrinolytic agent used in PI group	No.(%) Killip class I	HT n(%)	DL n(%)	FH of CVD n%	DM n(%)	Prior MI n(%)	Smoking current/ recent	No. of rescue PCI in PI group n(%)	Time-to-treatment	Outcomes reported
2016[343] *Canada* N=1216 Study period *2009 - 2011*	236 (19.4) PPCI 980 (80.5)	13.0	(72.9)		(90.4)	(48.0)	(43.6)		(17.2)	(14.0)	(43.3)		SONT/SOBT (IQR) PI NR PPCI 204 (141-312) Median (IQR) NBT (mins): 260 (201-385)	ACM, RI, CE, Stroke, ICH, TB, MaB, MiB
Carrillo 2016[344] *Spain* N=2470 Study period *2010 – 2012*	PI 243 (9.8) PPCI 2227 (90.2)	61.4 (13.3)	1990 (80.6)	Unknown dose TEN	2080 (84.6)	NR	NR	NR	442 (17.9)	229 (9.3)	NR	94 (38.7)	Median SONT/SOBT (IQR) PI 105 (78–139) PPCI 172 (136–215) Median (IQR) NBT (mins): NR	In hospital: CS, TB, 30 days: ACM
Andersson 2019[345] *US* N=27,205 Study period *2010 - 2016*	PI 1,278 (4.7) PPCI 25,927 (95.3)	61.58 ±12.85	18,963 (69.7)	NR	NR	18,831 (69.2)	16,665 (61.3)	4,563 (16.8)	7,028 (25.8)	6,018 (22.1)	12,294 (45.2)	758 (59.3)	Median SONT/SOBT (IQR) PI 115 (71-200) PPCI 168 (118-272) Median (IQR) NBT (mins): 223 (137-930)	In hospital: ACM, CS, RI, HF, ICH, TB

Key: ACM — all cause mortality; ADE — adverse drug event; ALT — alteplase; CE — composite endpoint; CM — cardiac mortality; CS — cardiogenic shock; CVD — cardiovascular disease; DL — dyslipidaemia; DM — diabetes mellitus; EARLY-MYO — Early Routine Catheterisation After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction; FH — family history; GRACIA-4 — Grupo de Análisis de la Cardiopatía Isquémica Aguda 4; HF — heart failure; HT — hypertension; ICH — intracranial haemorrhage; IQR — interquartile range; IS — ischaemic stroke; MaB — major bleeding; MI — myocardial infarction; MiB — minor bleeding; NBT —

needle-to-ballon time; NR — not reported; PI — pharmacoinvasive; PPCI — primary PCI; RBT — require blood transfusion; RET — reteplase; RH — re-hospitalisation; RI — re-infarction; SD — standard deviation; SOBT — symptom onset-to-balloon time; SONT — symptom onset-to-needle time; STR — streptokinase; STREAM — Strategic Reperfusion Early after Myocardial Infarction; SU — survival; TB — total bleeding; TEN — tenecteplase; TIA — transient ischaemic attack.

5.3.2.1 Study country

Of the five RCTs, one each was conducted in China,[329] Russia,[330] Spain[336] and Egypt.[335] The Strategic Reperfusion Early after Myocardial Infarction (STREAM) study, which was the largest included study (n=1,892 patients), was conducted across 15 countries (Austria, Belgium, Brazil, Canada, France, Germany, Greece, Italy, Norway, Peru, Poland, Russia, Serbia, Spain and the UK).[331]

Of the nine observational studies, two studies each were conducted in the US,[156, 345] Canada[341, 343] and India,[338, 342] and one study each was conducted in Russia,[337] Mexico[340] and Spain.[344] No RCT or observational studies were conducted in Ireland; hence, the applicability of these data to an Irish setting may be limited.

5.3.2.2 Study period

While the review was limited to studies published in 2008 or later, the age of the data used in the studies varied. For RCTs, the oldest data came from the STREAM study, where data collection commenced in 2008.[331] For observational studies, the oldest data came from Siontis et al., where data collection commenced in 2004.[156] The studies with the most recent data were Bendary et al.,[335] which was an RCT, and Sierra-Fragoso et al.,[340] which was an observational study. Both of these studies completed data collection in 2017. The duration of studies also varied greatly, ranging from six months[335] to four years[331] for RCTs and from one year[340] to eight years[156] for observational studies.

5.3.2.3 Funding source

Boehringer Ingelheim, who manufactures tenectplase and alteplase (fibrinolytic agents), provided funding for three studies.[329, 331, 338] AstraZeneca who manufactures ticagrelor (an antiplatelet agent that can be used as adjunctive therapy) provided part-funding for one study.[345] Governmental and health agencies provided funding (whole or in-part) for three studies.[336, 341, 345] Two studies reported that they received no external funding.[335, 342] Six studies did not disclose any funding sources.[156, 330, 337, 340, 343, 344]

5.3.2.4 Fibrinolytic agent

Tenecteplase was the most commonly used fibrinolytic agent among included studies (n=9),[156, 330, 331, 336-338, 341, 343, 344] followed by streptokinase (n=3),[330, 335, 342] alteplase (n=1)[329] and reteplase (n=1).[156] Tenecteplase was used exclusively in seven studies (two RCTs and five observational studies),[331, 336-338, 341, 343, 344] streptokinase was used exclusively in two studies (one RCT and one observational study),[335, 342] and one RCT used alteplase exclusively.[329] One observational study

allowed for clinicians to use either tenecteplase or reteplase at their discretion.[156] Another RCT allowed clinicians to use either tenecteplase or streptokinase at their discretion.[330] Two studies did not report which fibrinolytic agent was used.[340, 345]

Most studies (three RCTs and five observational) used full-dose regimens of the fibinolytic agent (n=8),[156, 331, 335-338, 341, 343] while two RCTs used half-dose regimens (n=2)[329, 330] and four observational studies did not report the dosing regimen used (n=4).[340, 342, 344, 345] Seventeen months into the STREAM study, the dose of tenecteplase was reduced by 50% in those aged 75 years or older because of an excess of intracranial haemorrhage (ICH) in this cohort.[331]

5.3.2.5 Adjunctive therapy

Adjunctive therapies are often administered before, alongside and after fibrinolytic agents or primary PCI to improve patient outcomes and are generally prescribed according to local protocols and international guidelines.[234] These adjunctive therapies include antiplatelet (aspirin and $P2Y_{12}$ inhibitors such as clopidogrel, prasugrel, cangrelor and ticagrelor), glycoprotein IIb/IIIa inhibitor (GPIs) (such as abciximab, eptifibatide and tirofiban) and anticoagulant agents (unfractionated heparin (UFH), low molecular weight heparin (LMWH) and bivalirudin).[346]

Adjunctive therapy protocols varied greatly between included studies and also between study arms (Appendix 3, Table A.11). However, in the majority of included studies that described their adjunctive therapy protocols (n=7), dual antiplatelet therapy with aspirin and clopidogrel (or the related ticagrelor)[329] was indicated for all patients, generally including an initial loading dose of these agents.[329, 330, 335, 336, 341-343] However, in one study, clopidogrel was only given to patients in the pharmacoinvasive arm and not to those who underwent primary PCI,[156] while in two other studies all adjunctive therapies (including antiplatelets and anticoagulants) were given to primary PCI patients according to local practices or at clinicians' discretion.[331, 338] Among included studies, UFH was the most commonly used anticoagulant (n=6),[156, 329, 330, 335, 341, 343] followed by LMWH (n=5)[331, 335, 336, 338, 341] and bivalirudin (n=1).[336] GPIs were not standard protocol in any included study; however, five studies explicitly permitted their use if clinicians felt their use was clinically indicated.[156, 329, 331, 335, 338] One of these studies only permitted the use of GPIs during or after catheterisation but not beforehand,[329] and another study only permitted their use for lesions with a heavy thrombus burden or where impaired coronary blood flow persisted after catheterisation.[335] Four studies did not describe their adjunctive therapy protocols.[337, 340, 344, 345]

5.3.2.6 Inclusion and exclusion criteria of included studies

The inclusion and exclusion criteria for each included study are outlined in Appendix

3 (Table A.12). In general, these criteria were more stringent for the RCTs compared with the observational studies, reflecting the 'real-world' nature of the observational studies.

The RCTs randomised patients so that they had an equal chance of being in either arm. However, a number restricted inclusion to patients where a PCI-related delay was expected,[329, 331] and, or to those who presented within a defined period (range 3-12 hours from symptom onset).[330, 331, 336] The STREAM study, which was the largest RCT, only enrolled patients who presented within three hours of symptom onset. Patients were subsequently excluded if it was expected that they could undergo primary PCI within one hour of diagnosis or if there was an inability to reach the catheterisation lab within three hours of diagnosis. After patients were randomised (median of 91 minutes from symptom onset), patients in the pharmacoinvasive arm received fibrinolysis in a median of nine minutes (inter-quartile range (IQR): 6-13), while patients in the control arm underwent primary PCI in a median of 77 minutes (IQR: 57-112). Hence the median symptom onset-to-reperfusion times in this study were 100 minutes (IQR: 75-143) and 178 minutes (IQR: 135-230) for the pharmacoinvasive and primary PCI arms, respectively.[331] Similarly, the Early Routine Catheterisation After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction (EARLY-MYO) trial only enrolled patients with symptom onset less than six hours at time of presentation. Patients were then eligible for inclusion if there was an expected delay in providing PCI of more than 90 minutes from first medical contact (FMC) and that this delay was at least 60 minutes longer than it would take to start fibrinoloysis. After randomisation (median 185-190 minutes from symptom onset), patients in the pharmacoinvasive arm started fibrinolysis in a median of 210 minutes (IQR: 166-270) from symptom onset compared with a median of 280 minutes (IQR: 214-340) from symptom onset to needle time for the primary PCI group.[329] Notably, patients with evolved STEMIs (defined as symptom onset > 12 hours)[234] were not eligible for inclusion in the RCTs. The studies differed with regards to the upperbound time limit for inclusion of patients; three hours in the STREAM study;[331] six hours in the EARLY-MYO[329] and Vyshlov et al.[330] studies; and 12 hours in the GRACIA-4 (Grupo de Análisis de la Cardiopatía Isquémica Aguda) study.[336] One RCT did not explicitly state an upperbound time limit for the duration of time from symptom onset to presentation.[335]

Absolute contraindication to fibrinolytic therapy was an exclusion criterion for all RCTs,[329-331, 335, 336] but was not an exclusion criterion for any of the observational studies as these patients would have received primary PCI (or no reperfusion therapy) instead. The contraindication criteria varied from study to study.

The following outlines the contraindications to fibrinolytic therapy in the EARLY-MYO

study[329]:

- definite cerebral apoplexy history
- any history of central nervous system damage or recent trauma to the head or cranium (< 3 months)
- active bleeding or known bleeding disorder/diathesis
- recent administration of any parenteral anticoagulation within 12 hours or current use of oral anticoagulation
- uncontrolled hypertension prior to randomisation
- major surgery, biopsy of a parenchymal organ, or significant trauma within the past two months
- prolonged or traumatic cardiopulmonary resuscitation (> 10 minutes) within the past two weeks
- major surgery pending in the following 30 days.

Cardiogenic shock was an exclusion criterion for all RCTs[329-331, 335, 336]; however, it was an exclusion criterion in only one observational study.[340] Two studies (one RCT[329] and one observational study[338]) excluded patients aged 75 years or older.

5.3.2.7 Study population

In total, 41,118 patients were included across all 14 studies (2,977 from RCTs and 38,141 from the observational studies). The RCT sample size ranged from 60[335] to 1,892 patients,[331] and for observational studies it ranged from 200[338] to 27,205.[345]

The studies reported median or mean ages of the study population: these ranged from 52[335] to 62[336] for RCTs and from 54[338] to 64 years[156] for observational studies. The majority of included patients were male, with the proportion ranging from 70%[330] to 89%[329] in RCTs and from 70%[345] to 86%[342] in observational studies. The prevalence of comorbid conditions in RCTs varied, specifically, hypertension ranged from 30%[335] to 51%,[329] dyslipidaemia ranged from 12% [335] to 88%,[330] diabetes mellitus ranged from 13%[331] to 32%,[335] and smoking (current/recent) ranged from 47%[336] to 68%.[335] The prevalence of comorbid conditions in observational studies also varied, specifically, hypertension ranged from 26%[342] to 85%,[344] dyslipidaemia ranged from 6%[338] to 94%,[337] diabetes mellitus ranged from 17%[337] to 51%,[338] and smoking (current/recent) ranged from 24%[338] to 65%.[156]. The majority of included patients underwent PCI with stenting ranging from 89%[336] to 95%[331] in RCTs and from 89%[342] to 95%[337] in observational studies. The proportion of patients in the pharmacoinvasive arm who underwent rescue PCI after failed thrombolysis ranged from 24%[329] to 40%[336] in RCTs and from 12%[338] to 59%[345] in observational studies.

The majority of included patients were at low risk of mortality, as indicated by the high prevalence of patients categorised as Killip class I (ranging from 65%[338] to 91%[337] in observational studies and from 93%[336] to 94% in RCTs).[331] Observational studies tended to have greater proportions of patients at higher risk of mortality (Killip classes II–IV), possibly reflecting the 'real-world' nature of these observational studies where patients with cardiogenic shock and other risk factors were included.

Important demographic differences were noted between the pharmacoinvasive and primary PCI arms in most of the observational studies, possibly reflecting 'real-world' allocation bias where the clinician will choose one treatment over another if he/she believes a high-risk subgroup will benefit from primary PCI and not a pharmacoinvasive strategy.[347] A notable difference in many of the observational groups was age, where patients undergoing primary PCI tended to be significantly older than their counterparts in the pharmacoinvasive strategy.[156, 337, 342, 344, 345] Some observational studies also found patients undergoing primary PCI were significantly more likely to have diabetes,[342, 345] hypertension[342, 345] or a higher mortality risk at baseline (Killip class),[338] compared with patients in the pharmacoinvasive arm (Appendix 3, Table A.11).

5.3.2.8 Time-to-treatment

The metrics used to measure time-to-treatment differed between studies (Appendix 3, Table A.11): ten studies reported symptom onset-to-balloon time (SOBT) [329-331, 335, 336, 338, 340, 343-345] (for primary PCI patients) and nine reported symptom onset-to-needle time (SONT)[329-331, 335-338, 344, 345] (for pharmacoinvasive patients). Five studies reported door-to-needle time (DNT);[156, 335, 338, 342, 343] five reported door-to-balloon time (DBT).[156, 335, 337, 342, 343] Two studies reported first medical contact (FMC)-to-needle time;[336, 344] three studies reported FMC-to-balloon time.[330, 336, 344] For RCTs, symptom onset-to-randomisation time (SORT) and randomisation-to-balloon time (RBT) were reported in three studies;[329, 331, 336] randomisation-to-needle time (RNT) was reported in two studies.[329, 331] A needle-to-balloon time (NBT) (relating to the delay between fibrinolytic administration and PCI balloon inflation for both patients undergoing rescue PCI and those undergoing PCI following routine angiography) was reported or estimatable for nine studies.[329, 331, 335-338, 342, 343, 345] The studies reported median or mean SOBT (range from 168[345] to 309 minutes[340]), SONT (range from 80[337] to 245 minutes,[338]), DBT (range from 39[340] to 105 minutes[342]), DNT (range from 28[156] to 47 minutes[338]), FMC-to-balloon time (range from 117[330] to 126 minutes[336]), FMC-to-needle time (range from 45[344] to 75 minutes[336]), SORT (range from 91[331] to 190 minutes[329]), RBT (range from 65[336] to 110 minutes[329]), RNT (range from 9[331] to 57 minutes[329]) and NBT (range from 223 minutes[345] to 1,104 minutes[342]), respectively. As expected,

timings in the pharmacoinvasive arms tended to be quicker than in the primary PCI arms, reflecting the ability to administer fibrinolysis prior to arriving at a PCI-capable centre.

5.3.2.9 Risk adjustment

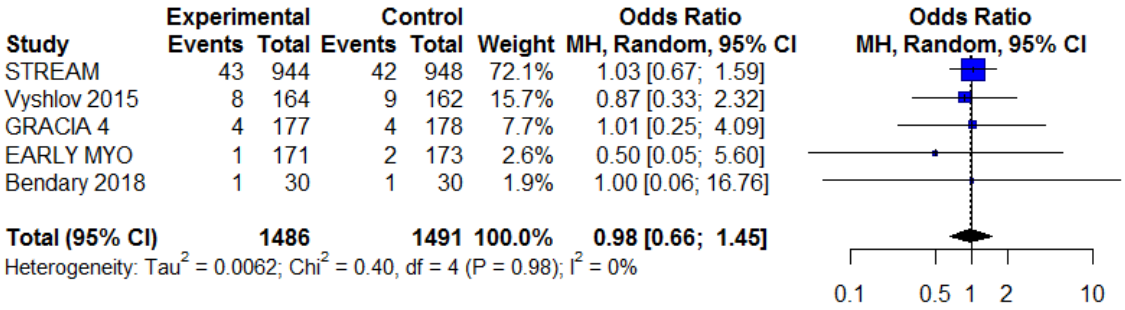
To meet the inclusion criteria of this review, all observational studies were required to report adjusted outcomes, controlling for important confounding factors that may have biased the results. Based on the literature[347] and discussions with the Steering Group, it was agreed that observational studies should ideally control for age, sex, co-morbidities and severity of disease. Four of the nine observational studies controlled for all four of these confounders.[156, 337, 344, 345] One study did not control for sex,[343] one did not control for severity (that is, Killip class),[342] one did not control for co-morbidities[338] and two did not control for sex or co-morbidities.[338, 340, 341] It is possible that these factors were not included in study's regression models because of collinearity; however, this reason was not given in any of these studies.

5.3.3 Primary effectiveness outcomes

5.3.3.1 All-cause mortality

All five RCTs [329-331, 335, 336] and three observational studies [156, 342, 344] reported all-cause mortality as an outcome (Table 5.3). A meta-analysis of in-hospital or 30-day all-cause mortality in RCTs, comparing the pharmacoinvasive strategy with primary PCI, found comparable outcomes between arms (OR: 0.98, 95% CI: 0.66-1.45, I^2 = 0%) (Figure 5.3). Two studies reported all-cause mortality at one year and likewise both studies found no significant between-group differences ((OR: 1.14, 95% CI: 0.79-1.65)[331] and (OR: 0.88, 95% CI: 0.31-2.47), respectively).[336] Time-to-treatment metrics were inconsistently reported in included studies, precluding any meaningful subgroup analysis to determine a specific cut-off time above which a pharmacoinvasive strategy would definitively provide better outcomes. Furthermore, it is important to stress that these findings must be interpreted within the context in which the trials were conducted. For example, the STREAM study was limited to those patients who presented within three hours of symptom onset and who could arrive at a cath lab within three hours of diagnosis, but for whom initial PCI-related delays were expected (that is, patients were excluded if it was expected that they could undergo primary PCI within one hour of diagnosis).[331] Importantly, the inclusion and exclusion criteria with regards timing differed slightly between studies (Appendix 3, Table A.12), but one other RCT explicitly excluded patients who were expected to undergo primary PCI within 90 minutes of FMC or a predicted diagnosis to balloon inflation time greater than three hours.[329]

Figure 5.3: Meta-analysis of all-cause mortality (in-hospital/30 days) - RCTs

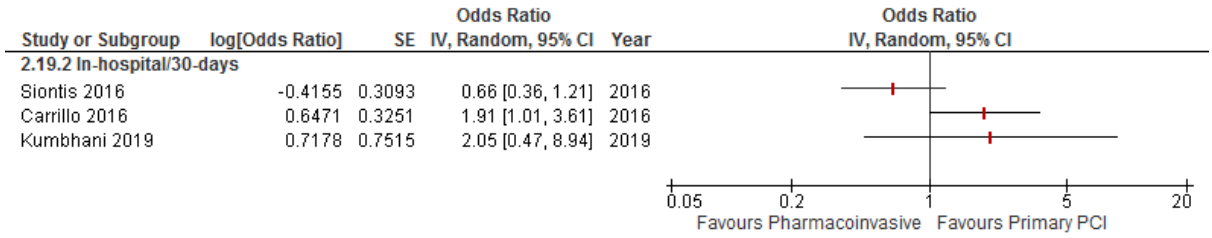


Key: CI — confidence interval; MH — Mantel–Haenszel.
Experimental group = pharmacoinvasive. Control group = primary PCI.

Due to safety concerns regarding an excess of ICH in patients age 75 years or older in the STREAM study, the dose of tenecteplase was halved for this patient group during the trial. Before the amendment, there was a significant excess of all-cause mortality in the pharmacoinvasive arm compared with the primary PCI arm (9.9% versus 4.3%; OR: 2.47, 95% CI: 1.05-5.79). However, after the protocol amendment, no statistically significant difference in all-cause mortality was found between the two arms (5.9% versus 6.3%, OR: 0.92; 95% CI: 0.60-1.41).[331, 334]

Pooling of effect estimates was not possible for observational studies due to the limited number of included studies (Figure 5.4).[156, 342, 344] The three observational studies reported adjusted ORs (and 95% CIs) for in-hospital or 30-day all-cause mortality of 0.66 (0.36–1.21),[156] 1.91 (1.01–3.50)[344] and 2.05 (0.47–8.94),[342] respectively (Table 5.3). Hence, two studies reported no significant association between reperfusion strategy and mortality,[156, 342] while Carrillo et al. reported a significant association between reperfusion strategy and mortality in favour of primary PCI, although the statistical significance was only marginal.[344]

Figure 5.4: Forest plot of observational studies comparing all-cause mortality (in-hospital/30 days) by reperfusion strategy



Key: CI — confidence interval; IV — inverse variance; SE — standard error.

Carrillo et al. conducted sensitivity analyses using propensity score adjustment and matching to control for imbalances in the distribution of patient characteristics between groups.[344] The authors found that the effect estimate became non-significant under these sensitivity analysis scenarios (OR: 1.71, 95% CI: 0.99–2.95 and OR: 2.21, 95% CI: 0.93–5.25, respectively).[344]

Long-term all-cause mortality was reported by Kumbhani et al.[342] and Siontis et al.[156] No significant association between reperfusion strategy and all-cause mortality was found at one year (OR: 1.12, 95% CI: 0.57–2.20),[342] at two years (OR: 1.12, 95% CI: 0.60-2.09)[342] or at five years (OR: 0.84, 95% CI: 0.63–1.12) (Table 5.3).[156, 342] However, caution is required when interpreting this finding as only two of the nine observational studies evaluated this outcome beyond 30 days.

5.3.3.2 Survival

One RCT[331] and one observational study[156] reported survival outcomes using Kaplan–Meier curves (Table 5.3). In the STREAM study, 63 patients (6.7%) had died in the pharmacoinvasive arm, compared with 56 (5.9%) in the primary PCI arm, after one year (OR: 1.14, 95% CI: 0.79-1.65). All-cause mortality rates tended to be similar during the first 30 days. Beyond the first month, all-cause mortality rates was higher for the pharmacoinvasive arm than for primary PCI; however, this was not statistically significant (log-rank p=0.495).[331]

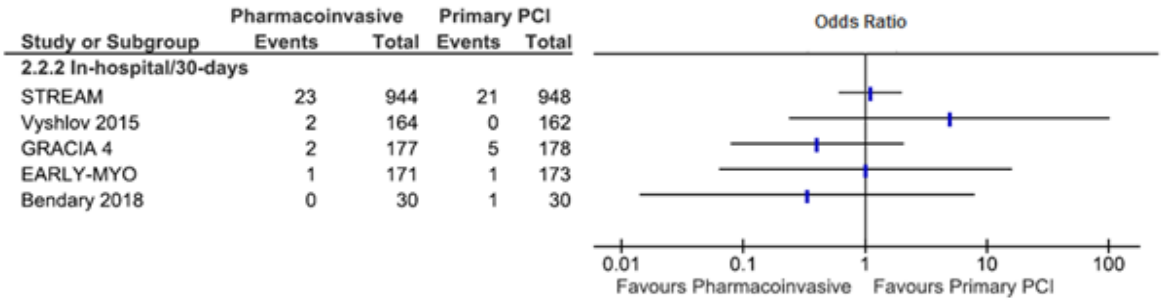
In the observational study by Siontis et al., the pharmacoinvasive strategy was associated with improved survival from the index STEMI until the end of follow-up (median follow-up of 3.9 and 4.4 years for the pharmacoinvasive and primary PCI groups, respectively) in univariate (hazard ratio (HR): 0.69, 95% CI: 0.52–0.92) but not in multivariate analysis (HR: 0.84, 95% CI: 0.63–1.12). Among 30 day survivors, the two strategies had comparable effects on all-cause mortality in both univariate and multivariate analyses. The magnitude of the effect difference between the two arms tended to be larger for early (≤ 30 days) (HR: 0.66, 95% CI: 0.36–1.21) compared with late (> 30 days) (HR: 0.92, 95% CI: 0.67–1.28) mortality; however, the difference was not statistically significant.[156]

5.3.3.3 Re-infarction

All five RCTs reported re-infarction as an outcome,[329-331, 335, 336] but no observational study reported this as an adjusted outcome. Due to the inclusion of studies with zero events in some arms, Bayesian meta-analysis using beta-normal hierarchical models was undertaken in statistical software R using the MetaStan programme. This meta-analysis of in-hospital or 30 day re-infarction in RCTs, comparing the pharmacoinvasive strategy with primary PCI, found comparable

outcomes between arms (OR: 0.97, 95% CI: 0.42–2.09) (Figure 5.5). Re-infarction at one year was reported in one study with no significant difference found between the two arms (2.8% vs. 4.5%, OR: 0.62, 95% CI: 0.20-1.93) (Table 5.3).[336] However, caution is required when interpreting this finding as only one study evaluated this outcome beyond 30 days.

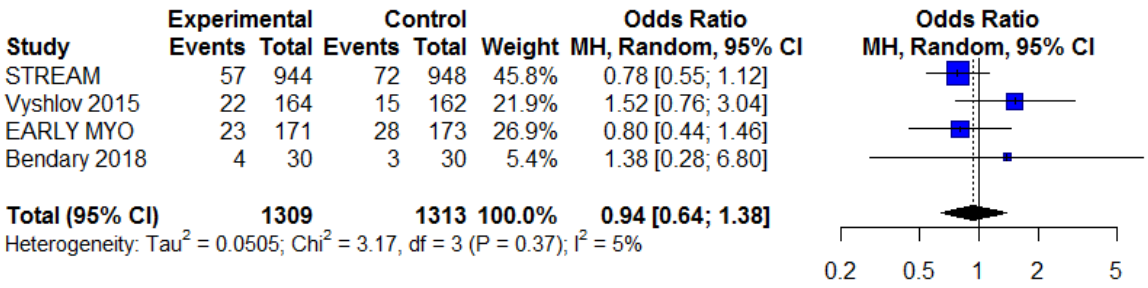
Figure 5.5: Meta-analysis of re-infarction outcomes (in-hospital/30 days) – RCTs



5.3.3.4 Heart failure

Four RCTs reported heart failure as an outcome,[329-331, 335] but no observational study reported this as an adjusted outcome. A meta-analysis of in-hospital or 30-day heart failure in RCTs, comparing the pharmacoinvasive strategy with primary PCI, found comparable outcomes between arms (OR: 0.94, 95% CI: 0.64-1.38, I^2 = 5%) (Figure 5.6). No study reported heart failure outcomes beyond 30 days.

Figure 5.6: Meta-analysis of heart failure outcomes (in-hospital/30 days) – RCTs

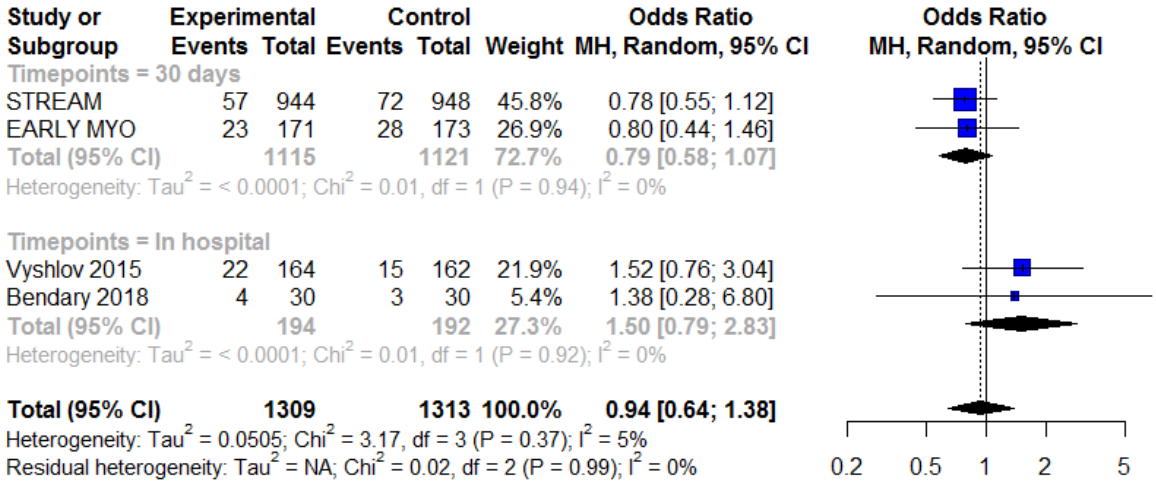


Key: CI — confidence interval; MH — Mantel–Haenszel.
Experimental group = pharmacoinvasive. Control group = primary PCI.

Notably, when the in-hospital and 30-day outcomes are separated, there is a trend

for more heart failure events in the pharmacoinvasive arm at the in-hospital timepoint. This trend is reversed at the 30-day timepoint, with more events in the primary PCI arm. However, this difference is not significantly different (P=0.08) (Figure 5.7).

Figure 5.7: Subgroup analysis of heart failure outcomes by timepoints



Key: CI — confidence interval; MH — Mantel–Haenszel.

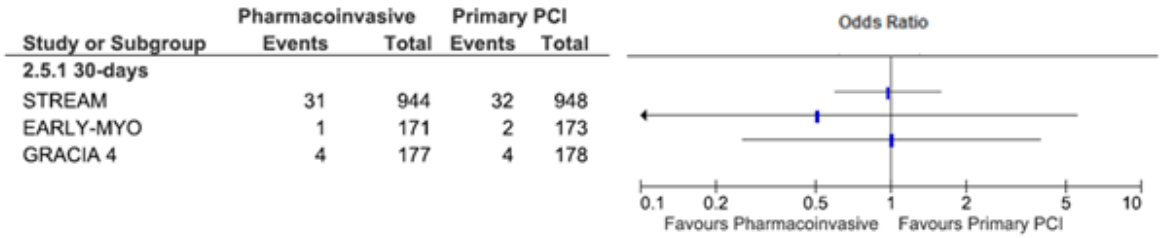
5.3.3.5 Cardiogenic shock

Only one RCT reported cardiogenic shock as an outcome (Table 5.3).[331] The STREAM study found that cardiogenic shock occurred in 4.3% of the pharmacoinvasive arm compared with 5.9% of the primay PCI arm at 30 days. Although there was a numerically higher event rate in the primary PCI group, this was not statistically different (OR: 0.72, 95% CI: 0.48-1.09). No study reported this outcome beyond 30 days. No observational study reported cardiogenic shock as an adjusted outcome.

5.3.3.6 Cardiac mortality

Three RCTs reported cardiac mortality as an outcome (Table 5.3).[329, 331, 336] No observational study reported it as an adjusted outcome.In all three RCTs, there was no difference in cardiac mortality between the pharmacoinvasive and primary PCI arms at 30 days (Figure 5.8). Cardiac mortality at one year was similar for both reperfusion strategies in the STREAM study: 4.0% and 4.1% for pharmacoinvasive and primary PCI, respectively (p = 0.93).[334] Cardiac mortality at one year was also similar for both reperfusion strategies in the GRACIA-4 study: 3.6% and 2.9% for pharmacoinvasive and primary PCI, respectively (p = 0.72).[336]

Figure 5.8: Forest plot of RCTs comparing cardiac mortality outcomes between pharmacoinvasive and primary PCI groups (30 days)

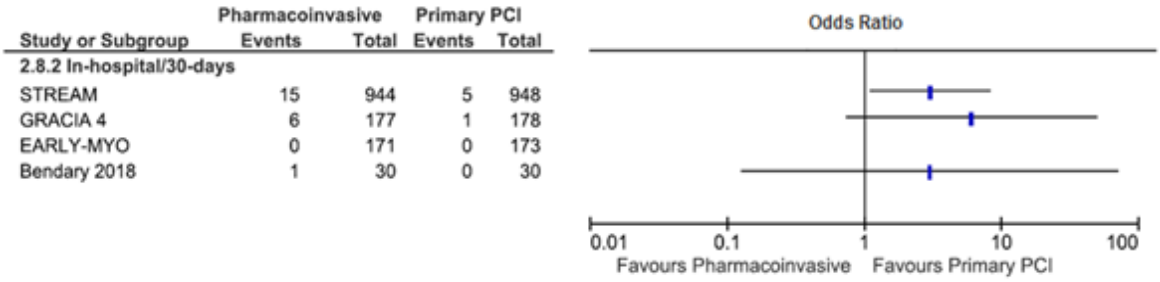


5.3.4 Primary safety outcomes

5.3.4.1 Total stroke

Four RCTs reported the total number of strokes (ischaemic or haemorrhagic) as an outcome (Figure 5.9).[331, 335, 336, 343] No observational study reported this as an adjusted outcome. Due to the inclusion of studies with zero events in some arms, Bayesian meta-analysis using beta-normal hierarchical models was undertaken in statistical software R using the MetaStan programme. This meta-analysis of in-hospital or 30 day total stroke in RCTs, comparing the pharmacoinvasive strategy with primary PCI, found that patients who were randomised to the pharmacoinvasive strategy had 4.26 times higher odds of having a stroke compared with patients who were randomised to primary PCI (OR: 4.26, 95% CI: 1.52–14.16). However, it is important to acknowledge the rarity of this event. There is only an absolute risk of 17 per 1,000 (1.7%) in the pharmacoinvasive arm compared with 5 per 1,000 (0.5%) in the primary PCI arm. The pooled effect estimate is driven largely by the STREAM study, which accounts for 15/22 (68.2%) and 5/6 (83.3%) of the total stroke events in the pharmacoinvasive and primary PCI arms, respectively.[331] Based on the calculated OR and 95% CIs, and assumed baseline risk of 0.45% a number needed to treat for an additional harmful outcome (NNTH) was estimated. For every 70 patients (95% CI: 16–433) treated with a pharmacoinvasive strategy instead of primary PCI, one additional stroke may occur. However, the wide confidence interval reflects the substantial level of uncertainty around the point estimate.

Figure 5.9: Meta-analysis of total stroke outcomes (In-hospital/30 days) - RCTs



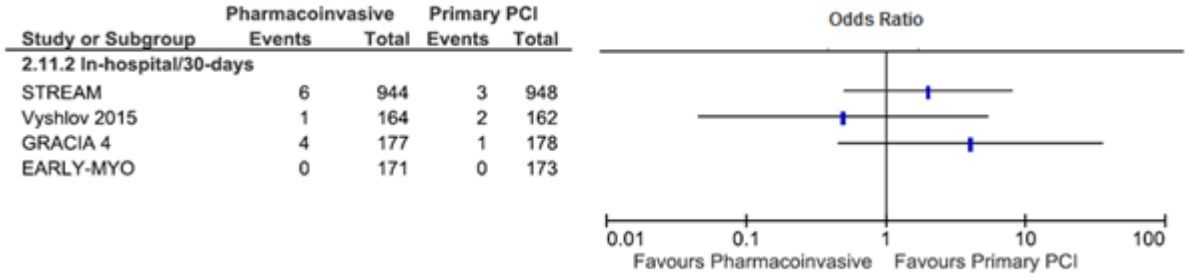
A sensitivity analysis was also conducted to examine the impact of using alternative meta-analysis statistical models on the overall pooled effect estimate, and broad consistency was found between the various approaches (Appendix 8).

One RCT reported total strokes at one year and found a significant treatment effect persisted at this time point in favour of primary PCI (4.5% vs. 0.5%, OR: 8.38, 95% CI: 1.04-67.71) (Table 5.3).[336] However, caution is required when interpreting this finding as this was the only study (RCT or observational) that evaluated this outcome beyond 30 days.

5.3.4.2 Ischaemic stroke

Four of the five RCTs reported ischaemic stroke as an outcome (Figure 5.10). No observational study reported this as an adjusted outcome. Due to the inclusion of studies with zero events in some arms, Bayesian meta-analysis using beta-normal hierarchical models was undertaken in statistical software R using the MetaStan programme. This meta-analysis of in-hospital or 30 day ischaemic stroke in RCTs, comparing the pharmacoinvasive strategy with primary PCI found comparable outcomes between arms (OR: 1.89, 95% CI: 0.56–6.17). Ischaemic stroke at one year was reported in one study, and no significant difference was found between the two groups (3.4% vs. 0.5%; OR: 6.21, 95% CI: 0.74-52.13) (Table 5.3).[336] However, caution is required when interpreting this finding as this was the only study to evaluate this outcome beyond 30 days.

Figure 5.10: Meta-analysis of ischaemic stroke outcomes (In-hospital/30 days) - RCTs

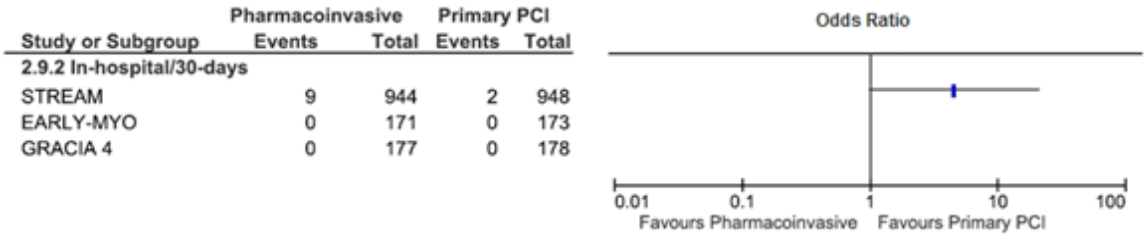


5.3.4.3 Intracranial haemorrhage

Three RCTs reported ICH as an outcome,[329, 331, 336] with zero events in two of the three studies (Figure 5.11).[331] In the STREAM study, the study protocol was amended to reduce the dose of tenecteplase by 50% in patients 75 years of age or older because of an excess of ICH in this age group pre-amendment (7.1% (n=3) vs. 0% (n=0)). After implementation of the dose reduction, no ICH events occurred in patients aged 75 years or older in either group.[332] However, these post-hoc observations are only hypothesis-generating and hence caution is required when interpreting these findings.

One year follow-up of ICH events was reported for only one RCT, the GRACIA 4 study, with still no event occurring in either group at this timepoint.[336] No observational study reported ICH as an adjusted outcome.

Figure 5.11: Forest plot of RCTs comparing ICH outcomes (in-hospital/30 days) by reperfusion strategy

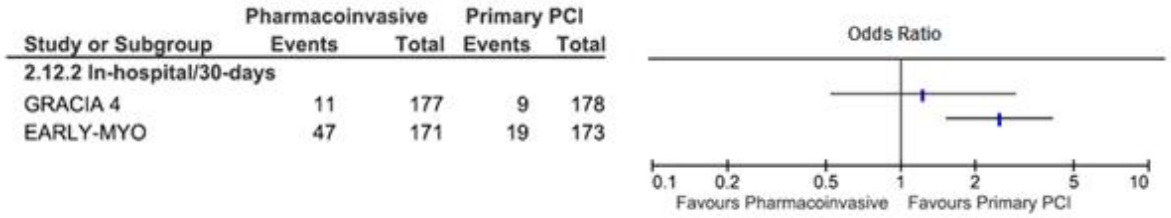


The rarity of this outcome is evident when the absolute numbers of ICH events from the observational studies are examined. Of the five observational studies that reported this outcome,[156, 338, 341, 343, 345] ICH occurred in only 15 of a total of 2,563 (0.5%) patients in the pharmacoinvasive arm compared with 36 of a total of 28,792 (0.1%) patients undergoing primary PCI.

5.3.4.4 Total bleeding

Two RCTs reported total bleeding as an outcome (Figure 5.12) with one observational study reported total bleeding as an adjusted outcome (Table 5.3).[345] In both RCTs bleeding events occurred more frequently in the pharmacoinvasive arm; however, the difference was only significantly different in one study[329] (OR: 3.07, 95% CI: 1.72-5.50 vs OR: 1.24, 95% CI: 0.50-3.08). Long-term follow-up was conducted in one study at one year, and negligible differences were found between the two groups (7.9% vs. 7.3%). This is not surprising given that any bleeding event would most likely occur soon after administration of fibrinolysis.[336]

Figure 5.12: Forest plot of RCTs comparing total bleeding outcomes (in-hospital/30 days) by reperfusion strategy



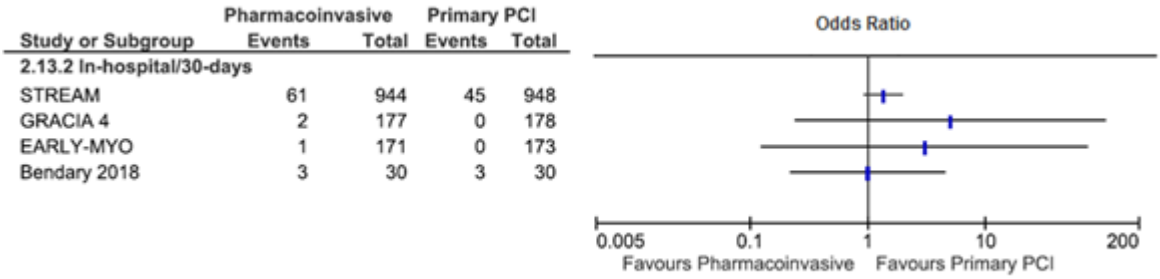
The sole observational study which reported in-hospital bleeding events as an adjusted outcome found the point estimate was in favour of the pharmacoinvasive strategy; however, the effect was not statistically significant (OR: 0.83, 95% CI: 0.65–1.07) (Table 5.3).[345] The study authors concluded that after adjusting for preprocedural bleeding risk and PCI access site (that is, femoral vs. radial), the rates of in-hospital bleeding were comparable between groups. The differences between the single RCT that reported a significant treatment effect[329] and the other two studies (one RCT and one observational study) which did not[336, 345] may potentially be explained by different definitions of bleeding used in the respective studies. An alternative explanation is differences in the fibrinolytic agent used. Neither the dose nor agent used was described in the Anderson study.[345] Alteplase, which is associated with a higher risk of bleeding compared with tenecteplase,[348] was used in the EARLY-MYO study, albeit at a half-dose.[329]

5.3.4.5 Major bleeding

Four RCTs[329, 331, 335, 336] and two observational studies[340, 343] reported major bleeding as an outcome (Figure 5.13). Due to the inclusion of studies with zero events in some arms, Bayesian meta-analysis using beta-normal hierarchical models was undertaken in statistical software R using the MetaStan programme. This meta-analysis of in-hospital or 30 day major bleeding in RCTs, comparing the pharmacoinvasive strategy with primary PCI, found comparable outcomes between

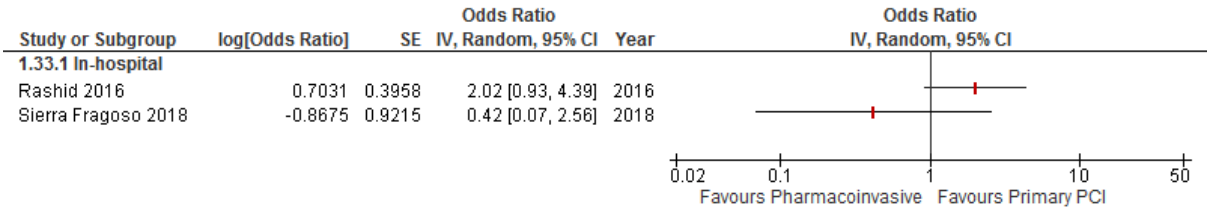
arms (OR: 1.61, 95% CI: 0.78–4.44). Major bleeding at one year was reported in one study, and no significant difference was found between the two arms (1.1% vs. 0%, OR: 9.72, 95% CI: 0.51-4365.37).This is not surprising given that any bleeding event would be most likely to occur soon after administration of the fibrinolytic agent.[336]

Figure 5.13: Meta-analysis of major bleeding outcomes (in-hospital/30 days) - RCTs



Pooling of effect estimates was not possible for observational studies due to the limited number of included studies (Figure 5.14). These two observational studies reported adjusted ORs (and 95% CIs) for in-hospital major bleeding of 2.02 (0.93–4.41)[343] and 0.42 (0.07–2.56),[340] respectively. No significant association was found between reperfusion strategy and major bleeding in either study. However, the point estimates are not consistent with each other or with the pooled RCT effect estimate.[340]

Figure 5.14: Forest plot of observational studies comparing major bleeding outcomes (in-hospital) by reperfusion strategy



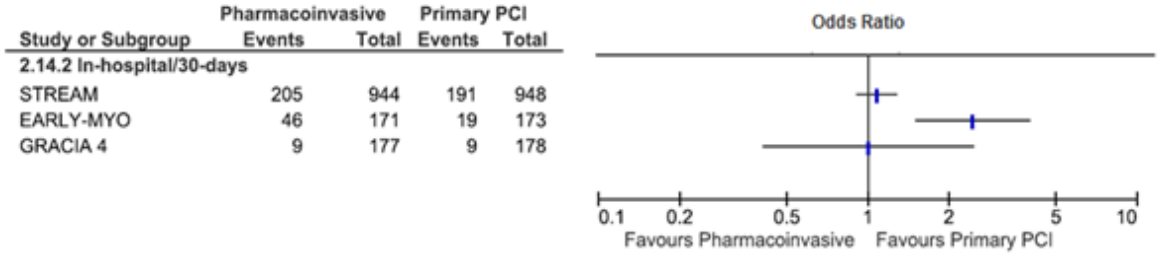
Key: CI — confidence interval; IV — inverse variance; SE — standard error.

5.3.4.6 Minor bleeding

Three RCTs reported minor bleeding as an outcome (Figure 5.15).[329, 331, 336] No observational study reported minor bleeding as an adjusted outcome. Although two studies showed no significant difference between groups,[331, 336] one study showed a substantially significant difference in favour of primary PCI (OR: 2.98, 95% CI: 1.66-5.35).[329] The differences observed may be explained by different bleeding

definitions used in these studies. Alternatively, the differences may be due to the use of alteplase in this study,[329] which has been found to be associated with an increased risk of major bleeding compared with tenecteplase. However a half-dose of this agent was used, which seems to contradict this finding.[348] Minor bleeding at one year was reported in one study, and no significant difference was found between the two arms (6.7% vs. 7.3%, OR: 0.92, 95% CI: 0.41-2.08[336]). This is not surprising given that any bleeding event would be most likely to occur soon after fibrinolytic administration.

Figure 5.15: Forest plot of RCTs comparing minor bleeding outcomes (in-hospital/30 days) by reperfusion strategy



5.3.4.7 Anaphylaxis and other adverse drug events

Only one RCT reported adverse drug events, including anaphylaxis (Table 5.3).[331] No observational study reported these outcomes. In the STREAM study, no significant difference was found between the two groups at 30 days (15.4% vs. 17.3%, OR: 0.87, 95% CI: 0.69-1.12).[331]

5.3.5 Subgroup and sensitivity analyses

The robustness of the results was checked by performing subgroup and sensitivity analyses (Appendix 8). With the exception of the sensitivity of the overall pooled effect estimate for total stroke outcomes highlighted in Appendix 8, the analyses indicated that none of the other pooled effect estimates were sensitive to change or were influenced by any particular subgroup or study. However, due to the limited number of included studies, these analyses were likely underpowered to detect an effect.

5.3.6 Secondary outcomes

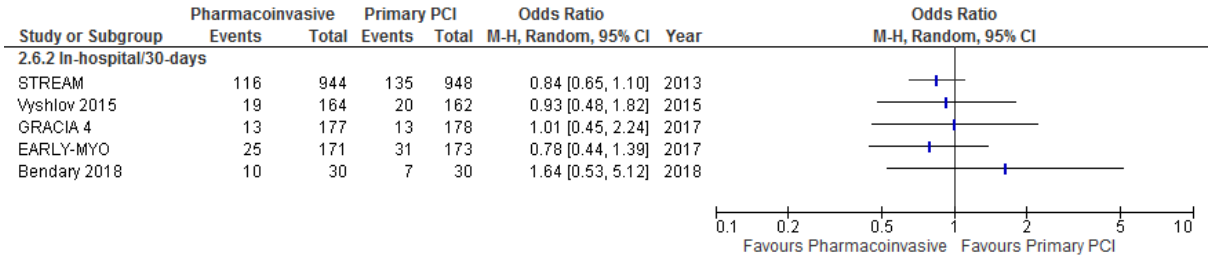
Composite and healthcare utilisation outcomes were the only secondary outcomes reported by included studies. No study reported health-related quality of life outcome.

5.3.6.1 Composite outcome

Due to the inconsistency in the definitions of the composite outcomes used in these studies, along with wider concerns regarding the use of composites in cardiovascular studies,[349] composite outcomes were not pooled. All five RCTs[329-331, 335, 336] and five observational studies [337, 338, 340, 341, 343] reported findings for a composite outcome. The individual outcomes used to define composite outcomes in these 10 studies included all-cause mortality (n=10),[329-331, 335-338, 340, 341, 343] re-infarction (n=10),[329-331, 335-338, 340, 341, 343] target vessel revascularisation (n=5),[335-338, 340] heart failure (n=4),[329, 331, 338, 341] cardiogenic shock (n=4),[330, 331, 338, 341] re-hospitalisation for cardiac causes (n=2),[335, 336] and major bleeding (n=2).[335, 336] Hence a variety of composite outcome definitions were used in these studies that often combined safety and effectiveness outcomes.

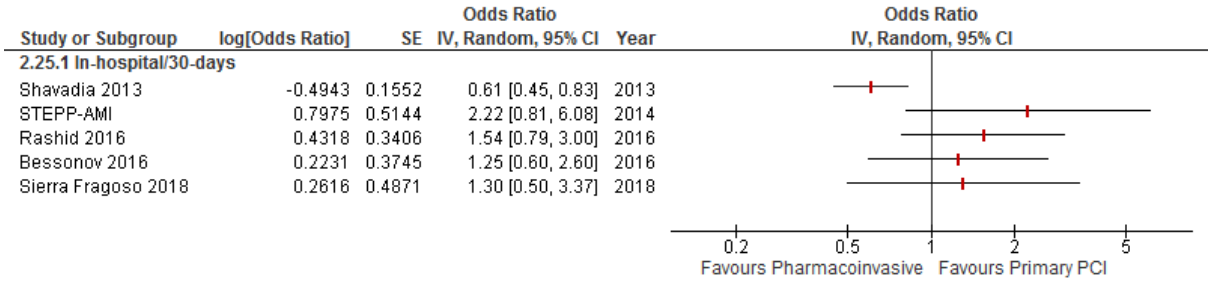
Although the results are not pooled for the reasons explained above, they are represented visually below (Figure 5.16 and Figure 5.17). All five RCTs and four of the five observational studies reported no significant difference in composite outcomes between the two groups (Table 5.3). One observational study reported a reduction in odds of 39% of the composite outcome in favour of the pharmacoinvasive arm (OR: 0.61, 95% CI: 0.45–0.83).[341] No obvious reason exists for this outlier result; however, it may be due to the presense of unidentified confounding variables in the dataset.

Figure 5.16: Forest plot of RCTs comparing composite outcomes (in-hospital/30 days) by reperfusion strategy



Key: CI — confidence interval; MH — Mantel–Haenszel.

Figure 5.17: Forest plot of observational studies comparing composite outcomes (in-hospital/30 days) by reperfusion strategy



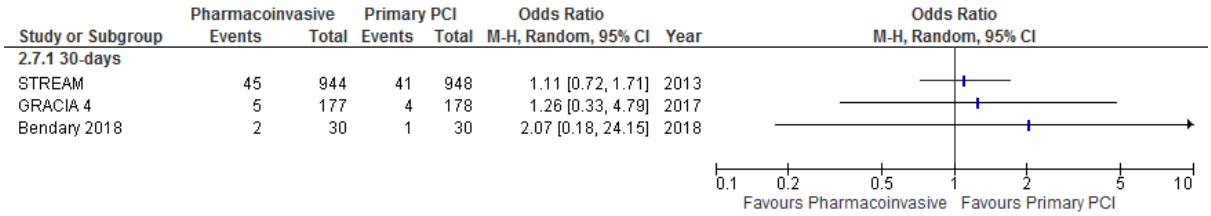
Key: CI — confidence interval; IV — inverse variance; SE — standard error.

Reporting of composite outcomes beyond 30 days occurred in one observational study (at three months, six months, one year and two years)[339] and in one RCT (at one year).[336] No significant difference was reported between arms at any stage.

5.3.6.2 Rehospitalisation for cardiac causes

Rehospitalisation for cardiac causes was reported in three RCTs,[331, 335, 336] but it was not reported in any observational study (Table 5.3). All three studies reported no significant between-group differences (Figure 5.18). Rehospitalisation for cardiac causes was reported at one year in one study, with no significant between-group difference found (OR: 1.16, 95% CI: 0.55-2.46).[336]

Figure 5.18: Forest plot of RCTs comparing rehospitalisation for cardiac causes (30 days) by reperfusion strategy



Key: CI — confidence interval; MH — Mantel–Haenszel.

5.3.7 Timing effects

Four studies (two RCTs[333, 336] and two observational[156, 344]) examined the impact of delays on the overall comparative effectiveness of the different reperfusion strategies. Carrillo et al. and the STREAM study both reported a significant association between reperfusion delays and patient outcomes.[333, 344] The observational study by Carrillo et al. found that delays less than 140 minutes (that is, 140 minutes or less between 'first medical contact' and initiation of primary PCI) were associated with significantly better mortality outcomes in favour of primary PCI.[344] Delays greater than 140 minutes (that is, 140 minutes or more between

'first medical contact' and initiation of primary PCI) resulted in comparable outcomes between the two groups.[344] The STREAM RCT found that PCI-related delays (that is, the time taken to receive primary PCI compared with immediate fibrinolysis) greater than 80 minutes were associated with significantly superior composite outcomes in the pharmacoinvasive arm. Delay times of less than 80 minutes (that is, 80 minutes or less between the initiation of primary PCI and the initation of fibrinolysis) resulted in comparable composite outcomes.[333] It must be noted, however that patients for whom it was expected PCI could be performed within 60 minutes from diagnosis were excluded fom this study as were those unable to arrive at the cath lab within three hours.

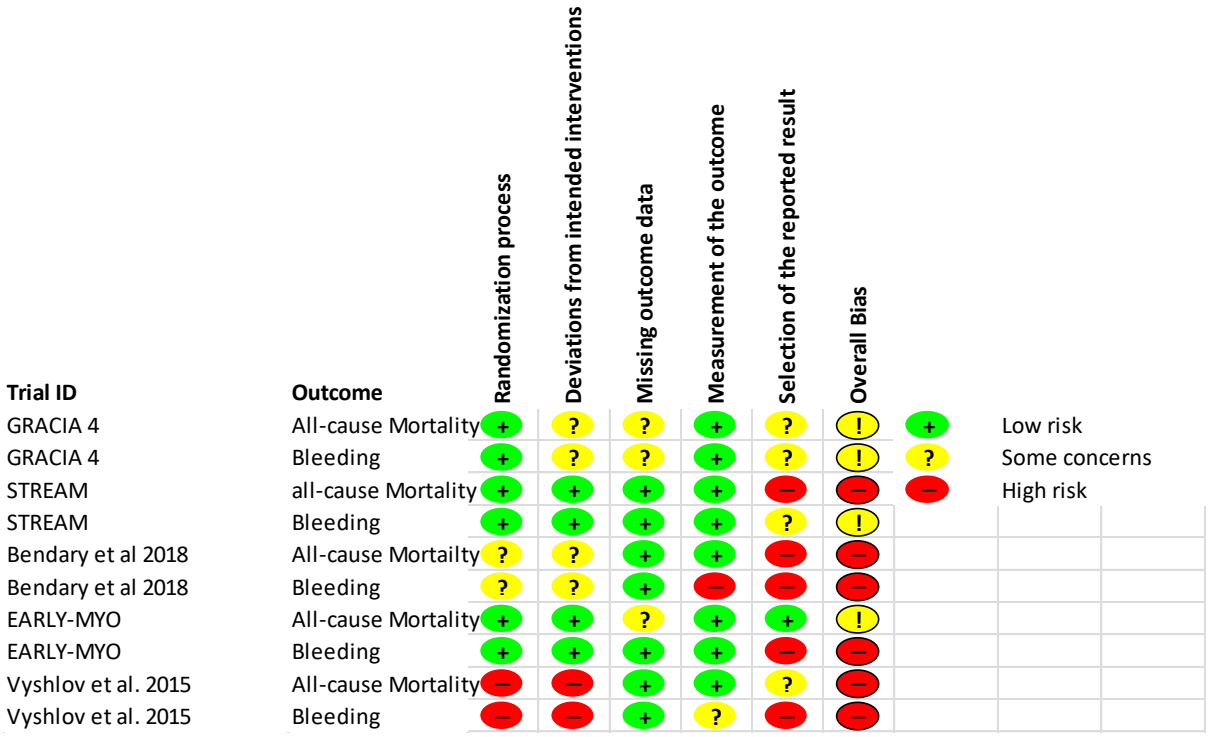
Two other studies examined the impact of different time-to-treatment metrics on the overall outcome and found no significant association.[156, 343] Subgroup analyses conducted for this review question also did not indicate any significant association between mean or median study time-to-treatment metrics (symptom onset-to-needle time (SONT) for the pharmacoinvasive strategy and symptom onset-to-balloon-time (SOBT) for primary PCI); however, due to the limited number of studies included, these analyses were likely underpowered to detect an effect (Appendix 8).

5.3.8 Methodological quality of included studies

5.3.8.1 Randomised controlled trials

The new Cochrane RoB 2.0 risk of bias tool recommends that assessments of risk of bias should be conducted at the outcome-level rather than at the study-level[326]; therefore, two outcomes per study were selected, resulting in 10 unique risk of bias assessments (Figure 5.19). Using this tool, the overall risk of bias was judged as 'some concerns' for four outcome-level assessments across three RCTs[329, 331, 336] and 'high risk' for the remaining six outcome-level assessments across four RCTs.[329-331, 335] The in-built algorithm in the RoB 2.0 tool automatically downgrades the overall risk of bias domain to match the lowest scored of the five individual domains. However, the review authors do not necessarily agree that this calculated 'overall bias' reflects the true risk of bias for all of these studies.[329, 331, 336] Therefore, it may be advisable to consider each individual domain in turn rather than the 'overall bias' domain when judging the risk of bias.

Figure 5.19: Risk of bias summary: review authors' judgements about each risk of bias item for each included RCT study, by outcome



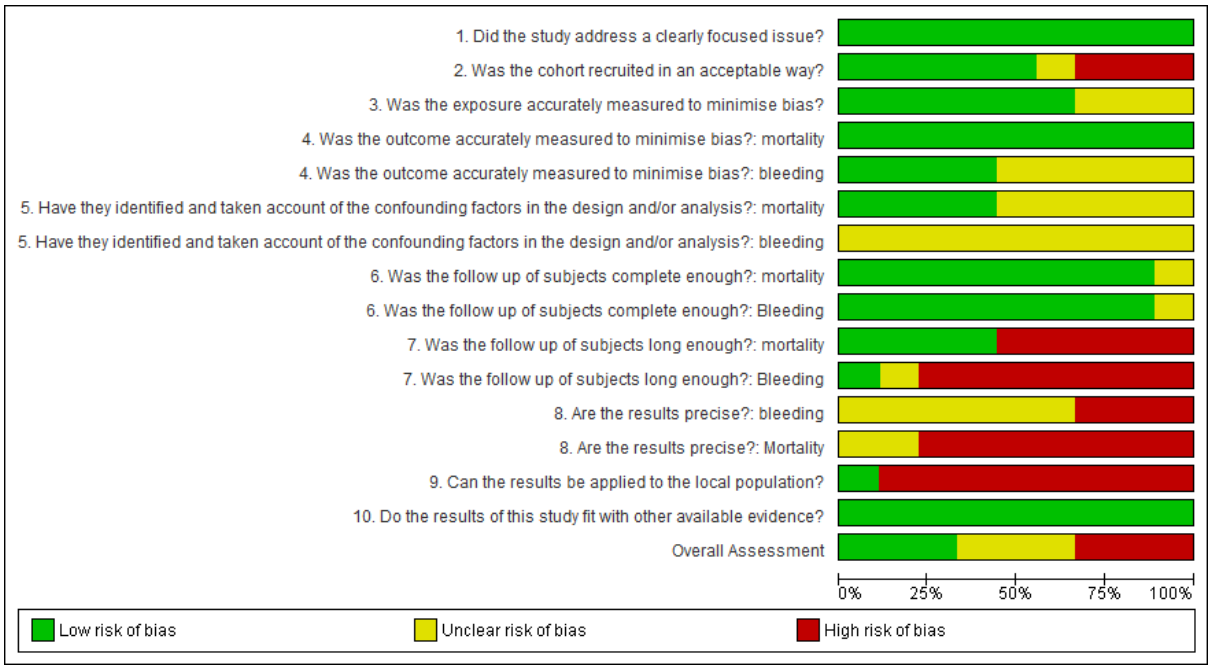
Three studies were judged to be at low risk in terms of the randomisation process,[329, 331, 336] one study was judged to have some concerns due to insufficient information describing this process[335] and another study was judged to be at high risk due to the use of open envelopes and, hence, the potential for allocation bias.[330] Two studies were judged to be at low risk in terms of deviations from intended interventions,[329, 331] two were judged to have some concerns due to potential issues with recruitment[336] and data analysis,[335] and one study was judged to be at high risk due to serious concerns with data analysis.[330] Missing outcome data was generally judged to be at low risk of bias;[329-331, 335] however, there were some concerns regarding how the study authors dealt with loss to follow up.[329, 336] Measurement of the outcome was generally judged to be at low risk of bias;[329-331, 335, 336] however, one study outcome was judged to have some concerns regarding the unblinded nature of outcome adjudication[330] and another study outcome was judged to be at high risk of bias due to the potential for the adjudicated severity of bleeding outcomes to be influenced by knowledge of intervention received.[335] All studies scored poorly in terms of selection of the reported result. Some concerns were raised in relation to late registering of or potentially significant changes to the protocol, but it was unclear the impact of these changes on the overall result.[329, 331, 336] Some study outcomes were judged to be at high risk of bias in this domain due to selective reporting issues such as promotion

of the composite endpoint to become the primary outcome midway through the trial,[331] outcomes presented in potentially misleading ways,[330, 335] and use of different measurement tools from what was documented in the protocol.[329]

5.3.8.2 Observational studies

Using the CASP quality appraisal tool,[314] three studies were judged to have an overall low risk of bias,[156, 344, 345] three were judged to have an unclear risk of bias[341-343] and three were judged to have a high risk of bias (Figure 5.20).[337, 338, 340]

Figure 5.20: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included observational studies, by outcome and by study



Most studies were considered at low risk of bias in the following domains (Figure 5.20):

- addressing a clearly focused issue (for example, clear aims/objectives)[156, 337, 338, 340-345]
- accurate measurement of outcome (for example, mortality outcomes retrieved in a consistent manner)[156, 337, 338, 340-345]
- completeness of follow-up (for example, minimal loss to follow up)[337, 338, 340-345]
- goodness of fit of results with other available evidence (for example, results do not completely contradict other studies).[156, 337, 338, 340-345]
- recruitment of cohort (for example, very broad and representative inclusion

criteria and minimal exclusion criteria)[156, 337, 341, 343-345]

- measurement of exposure (for example, clear protocols and definition of two treatment arms)[337, 338, 340-342, 344, 345]

However, the following domains were considered at high or unclear risk of bias in the majority of studies:

- length of follow-up (for example, in-hospital mortality only)[337, 340-345]
- imprecision of results (for example, very wide confidence intervals)[156, 337, 338, 340-345]
- applicability of results to the local population (for example, North American, Mexican, Russian or Indian studies are not necessarily applicable to the Irish setting).[156, 337, 338, 340-343, 345]

5.3.9 Certainty of the evidence

The overall certainty of the evidence was assessed and a summary of findings table was created using GRADEpro software[286] for each of the 17 primary outcomes, with RCTs and observational studies assessed separately. Evidence from meta-analyses was used to complete the assessment where appropriate, while a narrative synthesis was used to complete the assessment for the remaining outcomes.

Overall, the certainty of the evidence is 'low' to 'very low' due to the risk of bias across many included studies, some concerns regarding the imprecision and inconsistency of results and the observational nature of some included studies. The full summary of findings table is located in Appendix 9.

5.3.10 Ongoing studies

Three potentially relevant ongoing or just completed studies were identified through searching of the clinical trial registries. The Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction (STREAM-2) (NCT02777580) RCT study is related to the current STREAM study[331] and aims to compare the impact of a pharmacoinvasive strategy (using half-dose tenecteplase in patients 60 years or older with STEMI) with primary PCI. Two other observational studies were identified which aim to provide large registry-based evidence comparing primary PCI and pharmacoinvasive strategies in a Mexican setting (NCT03974581) and a Brazillian setting (NCT02090712).

5.4 Discussion

This systematic review and meta-analysis of contemporary research (studies published since 2008), found low- to very low-certainty evidence, suggesting that

where PCI-related delays are expected, but symptom onset does not exceed 12 hours, a pharmacoinvasive strategy may have comparable effectiveness to primary PCI. Furthermore, evidence suggests that within this context (that is, restricted to patients with initial expected delays in accessing PCI), timely treatment with a pharmacoinvasive strategy may be more effective than delayed primary PCI where the time difference exceeds 80 minutes.[333] However, this review also found low- to very low-certainty evidence of potential, albeit uncommon, safety concerns with a pharmacoinvasive strategy. Specifically the concerns related to minor bleeding (which is driving total bleeding events) and ICH (which is driving total stroke events). For every 70 patients treated with a pharmacoinvasive strategy instead of primary PCI, it is estimated that one additional stroke may occur; however, there is a substantial level of uncertainty around the point estimate (NNTH: 70, 95% CI: 16–433). No significant differences were found between groups in terms of the risk of ischaemic stroke or major bleeding. Evidence from observational studies included in this review suggested that, after adjusting for important confounders, no significant differences were observed between the two strategies in terms of mortality, total bleeding or major bleeding; however, it is noted that the relationship between reperfusion strategy and ICH or total stroke were not evaluated in these observational studies.

Due to the limited number and the small sample size of some of the included studies, the relatively low frequency of some of the endpoints under investigation, and some concerns regarding the risk of bias, these findings must be interpreted with caution. There are limited data to determine the pooled effect estimate and absolute effect measures for several of the outcomes under investigation. The data are also limited to patients presenting within 12 hours (and sometimes three hours) of STEMI onset. The majority of included studies focused on composite outcomes to compensate for the relatively small sample sizes of these studies[329-331, 335-338, 340, 341, 343]; these composite outcomes are less useful clinically than the individual effectiveness and safety components. Given the variation in the outcomes included as part of the composites, it is not possible to synthesise the data or compare between studies.[349] Furthermore, there are limited data to draw any definitive conclusions regarding a specific PCI-related delay time beyond which a pharmacoinvasive strategy may become more beneficial. However, the evidence supports the current ORS protocol for Ireland, which recommends that patients who can be transferred to a primary PCI centre within 90 minutes of STEMI diagnosis should undergo primary PCI, but if transfer within this timeframe is not possible then a pharmacoinvasive strategy should be considered.

An important observation from this review is that these studies were primarily conducted in large countries such as China,[329] Russia,[330] Spain[336] , Egypt,[335] the US,[156, 345] Canada[341, 343] India,[338, 342] and Mexico[340]. Smaller countries were

involved in the STREAM study (for example, Austria, Belgium, Greece, Serbia, and the UK), but no single study was conducted in a smaller country.[331] Furthermore, when classified using the Human Development Index (HDI), some of these countries would be classified as medium (India and Egypt) or high (China and Mexico), whereas Ireland and the majority of EU countries would be classified as very high.[36] As the significant investment required for establishment of a network of PCI-capable centres is often not possible in these low- and middle-income countries, the use of a pharmacoinvasive approach is viewed as a safe, effective and affordable option.[350] However, the pharmacoinvasive approach is also used in high-income countries. Many rural hospitals in such countries lack PCI facilities and not all PCI centres provide a 24/7 service; therefore, alternative STEMI care approaches are required. Many of these countries and regions (including Ireland, Catalonia, France, Austria and certain US states) have implemented a hybrid reperfusion strategy whereby primary PCI is the strategy of choice, but a fibrinolytic approach (often pharmacoinvasive) is available for patients with STEMI who are unable to undergo timely primary PCI.[113, 175, 344, 351, 352]

Conversely, certain smaller countries with a very high HDI (such as Northern Ireland and Denmark) have implemented a national primary PCI strategy (that is, all patients aim to get primary PCI) and have reported improvements in patient outcomes based on observational data.[91, 112, 152] Nationwide coverage with a primary PCI service requires extensive investment in PCI centres along with efficient emergency medical services (EMS) capable of rapidly accessing patients, diagnosing STEMI and transferring to PCI-capable centres as part of a well-organised STEMI network. The location of such PCI-capable centres is, therefore, critical; as discussed in RQ1, centres tend to be organised in a 'hub-and-spoke' formation.[33] From a financial and organisational perspective, it may be more feasible to implement a primary PCI strategy in high-income, smaller geographical countries and regions. However, another important consideration is the procedural volume for these PCI-capable centres because of the potential volume-outcome relationship discussed in RQ3. In other words, a low-volume PCI centre that serves a sparsely population region may provide timely access to primary PCI for patients living in that region; however, patient outcomes may be inferior to those achieved by a high-volume PCI centre located some distance away. Therefore, a hybrid reperfusion strategy may be suitable for high-income countries with patients living in remote regions where the procedural volume from any proposed PCI centre in that region would be too low to achieve optimal patient outcomes. However, provisions should be put in place to manage patients with absolute contraindications to fibrinolytic therapy. This issue has been addressed in other countries. For example, the Canadian Cardiovascular Society 2019 guidelines on the acute management of STEMI recommends in these hybrid reperfusion systems that each hospital within the network should have a

preplanned default initial reperfusion strategy (primary PCI or pharmacoinvasive) 'on the basis of geographic and transport considerations'.[212]

One of the main safety concerns with a pharmacoinvasive strategy is intracranial haemorrhage (ICH). The STREAM study published in 2013 implemented a mid-protocol amendment reducing the dose of tenecteplase by 50% in patients aged 75 years or older due to an elevated incidence of ICH in this cohort. Following the amendment, no subsequent ICH events occurred; reperfusion efficacy was not compromised.[331, 332] The current ESC guideline recommends that a half-dose of tenecteplase should be considered in patients 75 years of age or older.[234] The classification of this recommendation is IIa, meaning that the weight of evidence/opinion is in favour of usefulness/efficacy. Moreover, the recommendation is based on level B evidence, meaning that the data is derived from a single RCT, namely the STREAM study.[331] Although the EARLY-MYO study used half-dose alteplase, a significantly increased odds of minor bleeding was reported in the pharmacoinvasive arm compared with the primary PCI arm (OR: 2.98, 95% CI: 1.66-5.35);[329] no other study (using full or half-dose) found any significant differences in bleeding (major or minor) outcomes. Hence there is currently insufficient evidence to definitively recommend what dosing regimen provides optimal benefits, particularly in older patients; however, additional evidence is expected from the ongoing STREAM-2 study (NCT02777580), which compares primary PCI with a pharmacoinvasive strategy based on half-dose tenecteplase in patients 60 years or older.

Three systematic review and meta-analyses were conducted on this topic in recent years.[323-325] Although our results are largely in agreement with their main findings, particularly in support of a pharmacoinvasive strategy as a potential alternative to primary PCI when timely PCI cannot be guaranteed, some key differences were noted. A systematic review and meta-analysis by Liu et al. found three RCTs (including the STREAM study) published between 2006 and 2013 comparing 'early PCI' (that is, PCI within three to 24 hours of thrombolysis, which is analogous to the pharmacoinvasive strategy) with primary PCI.[324] The findings from this review were broadly comparable with our review for short-term mortality, re-infarction and major bleeding. However, while the magnitude of increased risk for major bleeding was comparable it was not statistically significant in our review based on the four RCTs included.

Siddiqi et al. conducted a systematic review and meta-analysis comparing a pharmacoinvasive strategy with primary PCI.[323] The authors found 17 relevant studies (six RCTs and 11 observational studies) published between 1994 and 2016. The meta-analysis of RCTs found a significant reduction in the odds of total stroke (OR: 0.41, 95% CI: 0.18–0.93), reinfarction (OR: 0.55, 95% CI: 0.30–0.99) and

haemorrhagic stroke (OR: 0.23, 95% CI: 0.06–0.81) in the primary PCI arm and a significant increased odds of cardiogenic shock in the primary PCI arm (OR:1.53, 95% CI: 1.08–2.18).[323] For all the other outcomes tested (all-cause mortality, likelihood of achieving TIMI-3 flow, ischaemic stroke and major bleeding), outcomes were found to be comparable. For the meta-analysis of observational studies, the only outcome that was found to have a significant treatment effect was all-cause (short-term) mortality, and this was found to be in favour of pharmacoinvasive strategy (OR: 1.39, 95% CI: 1.04–1.87). The results of our review would be somewhat in agreement with Siddiqi et al., particularly in relation to the meta-analysis of RCTs where an increased risk of total stroke and ICH associated with pharmacoinvasive strategies were identified. However, we found no evidence of an increased risk of reinfarction or a reduced risk of cardiogenic shock or mortality with a pharmacoinvasive approach. Furthermore, caution is required when interpreting the findings of the meta-analyses by Siddiqi et al, particularly the meta-analysis of observational studies due to the inclusion of older studies that used unadjusted event rates[353] and studies that would not meet the current definition of a pharmacoinvasive strategy.[351, 352, 354] As discussed in Section 5.3.2.7, within observational studies, there are generally significant demographic differences between patients who receive a pharmacoinvasive strategy and those who receive primary PCI; therefore, adjustment for key confounders such as age and baseline mortality risk is important.

Another systematic review and meta-analysis was conducted by Roule et al. that compared fibrinolysis conducted outside of PCI-capable centres with primary PCI.[325] This review included three large studies, published between 2002 and 2013. Notably, one of the included studies would be classified as 'faciliated PCI' approach (that is fibrinolysis administration with the intention of performing immediate PCI ≤ 2 hours after fibrinolysis administration) and, hence, would not have met our inclusion criteria due to its known detrimental effects.[321] The authors found that fibrinolysis was consistently associated with similar rates of short-term all-cause and cardiac mortality, a decreased risk of cardiogenic shock (RR: 0.67, 95% CI: 0.48–0.95), and an increased risk of total stroke (RR: 3.57, 95% CI: 1.39–9.17) and haemorrhagic stroke (RR: 4.37, 95% CI: 1.25–15.26). These findings are somewhat in line with our own findings; however we found insufficient evidence to suggest a protective effect of a pharmacoinvasive approach on cardiogenic shock.

Several large observational studies conducted in France,[355, 356] the US[357] and South Korea[354] were excluded from our review due to their use of routine coronary angiography more than 24 hours post fibrinolytic administration. These studies, therefore, did not meet the definition of a pharmacoinvasive strategy required for inclusion.[354-358] However, their findings are broadly in keeping with our review findings. All-cause mortality and survival rates were found to be comparable

between the fibrinolytic group and primary PCI in these particular studies.[354-357] However, one study reported that total stroke rates were comparable between the two groups (HR: 2.01, 95% CI: 0.37–10.99), which is in contrast with our finding of a significantly higher risk in the pharmacoinvasive group.[354] Furthermore, one study reported no significant difference between groups in terms of major bleeding (HR: 5.03, 95% CI: 0.59–43.15),[354] which is in line with our findings, while another reported a significant increase in major bleeding in the fibrinolytic group (OR: 1.17, 95% CI: 1.02–1.33).[357] These differences may be explained by the between country differences in the fibrinololysis protocols and their implementation as well as differences in the definition of major bleeding. Although some differences in results are noted, these 'real-world' findings from observational studies are largely in agreement with our own conclusions that fibrinolysis followed by early transfer to a PCI capable centre for angiography and PCI, if required, remains a suitable alternative when timely primary PCI is not an option.

The main strength of this study was the comprehensive search, in-depth analysis and confirmatory methods adopted by a team of reviewers experienced in the conduct of systematic reviews and meta-analyses. Furthermore, the assistance of a steering group with contextual knowledge and strong experience of performing and managing PCI added important clinical insights to this review.

One of the main limitations of this study was the limited number of studies and the relatively small study populations, which are likely underpowered to detect any clinically significant differences in key outcomes of interest. There were also some concerns regarding the risk of bias across most of the included studies. Advanced statistical methods were used to deal with the low event rates, particularly, zero event arms, in many of the included studies. Therefore, while the best available pooled effect estimates are presented here, caution is urged in their interpretation. More research is required to estimate the comparative effectiveness and safety of a pharmacoinvasive approach, particularly in the context of other advances in cardiology and changes to contemporary PCI practices. Time-to-treatment metrics were inconsistently reported in included studies, making comparisons challenging. Additionally the metrics reported in these studies are not necessarily routinely collected in practice, for example, symptom onset to balloon/needle time; therefore, translating these findings into practice may be difficult for health service providers and planners. Inconsistencies were also evident in the definitions used for various safety and composite outcomes in the included studies. Agreement is, therefore, required for these definitions to enable better between study comparisons and more clinically meaningful data syntheses.

In conclusion, this systematic review and meta-analysis suggests that a pharmacoinvasive strategy may be a suitable alternative to primary PCI when

primary PCI cannot be provided in a timely manner and symptom onset does not exceed 12 hours. However, there are some safety concerns with regards to a pharmacoinvasive strategy that, although infrequent, require appropriate contingency planning. Due to the limited number and small sample size of included studies and concerns regarding the risk of bias of included studies, these results should be viewed with caution. Furthermore, it is not possible to determine with any degree of certainty a specific cut-off time above which a pharmacoinvasive strategy would definitively provide better patient outcomes. The findings from this evidence review support the current ORS protocol for Ireland.

5.5 Key points

- A systematic review and meta-analysis was undertaken to compare the safety and effectiveness of a pharmacoinvasive strategy with primary PCI in adults diagnosed with STEMI.
- Of 1,825 unique records retrieved, 14 studies (five RCTs and nine observational studies) conducted in 20 countries were included. In total, 41,118 patients were included across all 14 studies (2,977 from RCTs and 38,141 from the observational studies).
- Overall, the certainty of evidence is 'low' to 'very low' due to the risk of bias across many included studies, concerns regarding the imprecision and inconsistency of results, and the observational nature of some included studies.
- The RCT data relate to patients in the early phase of STEMI at diagnosis (ranging from < 3 hours to < 12 hours from symptom onset) for whom an initial PCI-related delay is expected (60-90 minute delay before cath lab arrival). Within this context:
    - No significant differences were found between the two strategies in terms of all-cause mortality (OR: 0.98, 95% CI: 0.66–1.45), re-infarction (OR: 0.97, 95% CI: 0.42–2.09), heart failure (OR: 0.94, 95% CI: 0.64–1.38), ischaemic stroke (OR: 1.89, 95% CI: 0.56–6.17) and major bleeding (OR: 1.61, 95% CI: 0.78–4.44). Though not subject to meta-analyses, no differences were apparent between groups in terms of long-term survival, cardiogenic shock, cardiac mortality, anaphylaxis/adverse drug events, composite outcomes and rehospitalisation for cardiac causes.
    - Patients who were randomised to the pharmacoinvasive strategy had 4.26 times higher odds of having a stroke compared with patients who

were randomised to primary PCI (OR: 4.26, 95% CI; 1.52–14.16). Hence, one additional stroke may occur for every 70 patients patients treated with a pharmacoinvasive strategy instead of primary PCI (NNTH: 70, 95% CI: 16–433). Though not subject to meta-analyses, ICH, minor bleeding and total bleeding were found to occur numerically more frequently in the pharmacoinvasive groups.

- The observational data were not subject to meta-analyses. No differences were apparent between groups in terms of all-cause mortality, except in one individual study where mortality outcomes marginally favoured primary PCI patients. No differences were apparent in terms of composite endpoints, except in one individual study where the outcome favoured the pharmacoinvasive strategy. No differences were apparent in terms of total bleeding or major bleeding.
- The pharmacoinvasive strategy may be a suitable alternative to primary PCI when the latter approach cannot be provided in a timely manner and symptom onset does not exceed 12 hours; however, some safety concerns exist with regards to a pharmacoinvasive strategy, particularly in older patients. Ongoing research is investigating the use of half-dose tenecteplase in older patients as a means of mitigating these safety concerns.
- The evidence supports the current ORS protocol for Ireland, which recommends that patients who can be transferred to a primary PCI centre within 90 minutes of STEMI diagnosis should undergo primary PCI, but if transfer within this timeframe is not possible then a pharmacoinvasive strategy should be considered.

6 Discussion

The main purpose of this evidence review was to synthesise evidence to inform the work of the National Review, which aims to recommend the best configuration for a national adult specialist cardiac service in Ireland. The planned service would comprise population-based regional specialist cardiac networks and network hospitals configured to achieve optimal patient outcomes at a population level with particular emphasis on the safety, quality and sustainability of care.

The three main objectives of the evidence review were to:

1. identify and describe existing models of specialist cardiac networks, focusing primarily on countries with the most relevance to the Irish healthcare system.

2. identify international best practice for centres providing PCI, and to examine the evidence underpinning these criteria

3. identify evidence on the safety and effectiveness of strategies for managing STEMI, including primary PCI and pharmacoinvasive approaches in centres without PCI-capability.

In light of discussions with the National Review's Steering Group, it was clear that the management of STEMI was one of the most time-critical components of a specialist cardiac service, and that evidence to inform configuration of PCI services is considered essential to inform deliberations for the National Review. The staffing, equipment and organisation of specialised interventional cardiology services capable of delivering PCI (and particularly primary PCI) will likely also fulfil the requirements for other complex and acute cardiac conditions. Therefore, it was agreed that PCI would be used as the exemplar procedure to develop the evidence to inform the design of the 'hub' of a 'hub and spoke' model.

The following four review questions were addressed by this evidence review:

RQ1. What international models for specialist cardiac networks exist that might be applicable to the Irish healthcare system?

RQ2. What organisational and service specifications do national or international guidance documents recommend for centres providing PCI for cardiac conditions in adults?

RQ3. What is the relationship between procedure volume and patient outcomes for PCI?

RQ4. What is the safety and effectiveness of a pharmacoinvasive strategy

compared with primary PCI for adults diagnosed with STEMI?

In RQ1, a broad range of specialist cardiac networks were identified. STEMI networks in particular dominated our findings. Many of the identified networks were organised into 'hub and spoke' models that centralised specialist services into a high-volume PCI-capable 'hub', typically, but not always organised as a 24/7 service, with 'spoke' centres providing referral and triage pathways supported by a coordinated EMS system with shared, defined protocols. Networks identified in Emilia-Romagna, Catalonia and England may provide relevant information for the development of Irish specialist cardiac networks.

Of the identified ACS-related networks, the population served per 24/7 PCI centre ranged from 120,000 to 2.5 million inhabitants with the majority serving catchment areas with a population of between 300,000 and 1.1 million inhabitants. This has been suggested as an 'optimal' catchment size range based on a survey of 30 European countries published in 2010. The authors of the survey estimated that a catchment population within this range would result in the region of 200 – 800 primary PCI procedures per year per centre, which they argued would be sufficient to sustain a high-volume of PCI procedures. The survey data reflected national practice in 2007 to 2008; national data from 2005 or 2006 were used in a number of instances where more recent data were not available.[194] The catchment size estimates may therefore be impacted by changes in the requirement for primary PCI rates due to changes in the incidence of STEMI.

As described in RQ1, there are nine PCI-capable centres in Ireland. Six of these centres are designated primary PCI centres, five of which operate on a 24/7 basis, with one operating from 9am-5pm Monday to Friday. A 24/7 service in Derry is contracted for the Donegal catchment. On the basis of 2016 census population data of 4.6 million inhabitants (excluding Donegal),[182] , this would suggest a crude national catchment population of 511,000 inhabitants per PCI-capable centre, or 920,000 inhabitants per 24/7 PCI centre. The exact catchment population served by each designated primary PCI centre in Ireland is challenging to calculate though as the flow of patients does not necessarily follow hospital group boundaries.

Furthermore not every hospital group has a primary PCI centre and some are served by more than one centre for geographical reasons. However, based on the latest operational plans for the six acute adult hospital groups,[359-364] as well as the Herity report,[365] we can estimate that only one designated primary PCI centre (with an estimated catchment population of approximately 286,000 in 2016), has less than the suggested minimum optimal catchment population of 300,000 inhabitants. The catchment area of the five other primary PCI centres range from approximately 400,000 to over one million inhabitants. Although this particular designated primary

PCI centre does not meet the suggested threshold of 300,000 inhabitants, it must be acknowledged that this minimum standard is primarily based on the assumption that a higher volume is associated with better patient outcomes.[194] As we determined in RQ3, this inverse volume-outcome relationship for PCI persists yet is based on 'very low' certainty of evidence. Furthermore, we determined that based on the huge variation in how low- and high-volume were defined among included studies, it was not possible to determine a specific minimum volume threshold for PCI procedures.

On the upper end of the scale, the 2010 European survey by Widimisky et al. suggests a limit of approximately 1.1 million inhabitants per primary PCI centre due to practical concerns around congestion and overcrowding in centres at higher volumes.[194] As evident from international STEMI networks, 'spoke' hospitals with CCU facilities were required for repatriation of patients post PCI procedures to reduce pressures on the primary PCI 'hub' as well as locating patients closer to their own residence.[41] Important considerations in the Irish context are the general ongoing concerns regarding hospital overcrowding[366] and the fact that 28% of acute hospitals do not have a dedicated CCU, which may restrict options for repatriation of PCI patients post procedure.[367]

Appropriate staffing and facility resourcing of both 'hub' and 'spoke' hospitals are necessary to ensure safe, effective, efficient and sustainable operation of any proposed STEMI network. Staffing is a key issue with regard to specialist cardiac networks.[368] However, evidence on the most efficient use of staffing within a specialist cardiac network is lacking. Although some guidance documents in RQ2 reported specific recommendations, these varied hugely depending on the jurisdiction and appear to be based on local policy rather than being underpinned by any empirical research. Considerations included minimum operator procedure numbers to maintain competence and staff rest times, which presumably are informed by working time directives and usual staff contractual arrangements. Furthermore, staffing rosters may be organised to minimise the time spent by individual staff members in cardiac catheterisation laboratories given the significant occupational health risks associated with long-term ionising radiation exposure.[272] The reporting of staffing levels was inconsistent and heterogeneous for any identified specialist cardiac network in RQ1 and hence these data were not extracted. Therefore there is currently insufficient evidence to support any particular staffing configuration. However, consideration must be given to the recruitment and retention of adequate numbers of staff with sufficient expertise in order to meet international best practice and maintain competence, particularly for low-volume 24/7 PCI centres.

Distance and time are other important considerations, given the time-sensitive nature of STEMI in particular.[12] The average maximum distance between 'hub' and

'spoke' hospitals across the ACS-related networks identified in the review was approximately 113km. There is strong evidence to support PCI as first line treatment (primary PCI) for patients with STEMI when delivered by experienced providers within an expedited time frame. [27-30, 281] However this has to be balanced with safety concerns (that is, the suggestion that there are higher odds of mortality) associated with low-volume PCI hospitals and operators, which we found to persist, albeit the evidence was of 'very low' certainty. For patients that live beyond a certain distance from designated primary PCI centres, the focus should be on the provision of the optimal reperfusion strategy which may comprise a pharmacoinvasive strategy. Hence the location of the patient is an important factor with regards the delivery of an ACS network, and the optimal reperfusion service as implemented in Ireland since 2013 aims to balance the mortality benefits of primary PCI with the need to deliver thrombolysis to patients in more remote regions.[175]

In RQ4, we found evidence suggesting that a pharmacoinvasive strategy, as currently described in the HSE model of care for STEMI patients, has comparable effectiveness to primary PCI, where initial PCI-related delays are expected. Furthermore, evidence suggests that within this context (that is, restricted to patients with initial expected delays in accessing PCI), timely treatment with a pharmacoinvasive strategy may be more effective than delayed primary PCI where the time difference to treatment exceeds 80 minutes. However, we also found low- to very low-certainty evidence of some safety concerns with a pharmacoinvasive strategy, specifically regarding minor bleeding (which is driving total bleeding events) and ICH (which is driving total stroke events). It should be noted that these events were uncommon. This evidence is based on literature published since 2008 and should, therefore, reflect contemporary cardiac care. The data are limited to patients whose symptoms onset does no exceed 12 hours, so do not apply to patients with an evolved STEMI. It is also noted that the certainty of evidence for both the safety and effectiveness outcomes is rated as low to very low based on the GRADE assessment.

As noted, the optimal reperfusion strategy in Ireland is primary PCI if transfer to a primary PCI centre within 90 minutes of STEMI diagnosis is possible. Additional key performance indicators are in place for a cath lab door-to-balloon time of 30 minutes, suggesting a total time from STEMI diagnosis-to-balloon time of 120 minutes. If this is not possible, patients should be transferred to the nearest emergency department to commence fibrinolysis as part of a pharmacoinvasive strategy. Evidence from this review supports this optimal reperfusion service (ORS) protocol. In 2016, there were 1,412 confirmed STEMI cases in Ireland. The majority of these cases were treated with primary PCI (83.4%, n=1,177), some received no reperfusion therapy due to contraindications or other reasons (13.3%, n=188), and a minority received fibrinolysis (3.3%, n=47). This meant that of those receiving

reperfusion therapy, 96.2% underwent primary PCI and 3.8% were treated with fibrinolysis. Nationally, 71% of patients undergoing primary PCI were treated within the 120 minute window, ranging from 56 to 84% for designated primary PCI centres.[177] Of patients undergoing fibrinolysis, it is not known what proportion were transferred to a primary PCI centre for rescue PCI or who underwent angiography and PCI (if necessary) within 3–24 hours of thrombolysis.

Optimising patient outcomes requires timeliness across the full window, including timely recognition of symptoms at the patient and community level to improve time to first medical contact and STEMI diagnosis and improved direct and inter-hospital transfers and in-hospital windows. For patients outside the 90 minute drivetime window, there is a balance to be achieved between the additional benefits that can be achieved from faster reperfusion from prompt initiation of a pharmacoinvasive strategy with the possibility of increased harms associated with fibrinolysis. To quantify the potential for harm, we can use Irish data for the number of STEMI patients treated with thrombolysis in 2016 (n=47) and the calculated NNTH of 70 (95% CI: 16-433). Assuming a similar baseline risk of stroke exists in the Irish STEMI population (0.45%) and that these patients received a pharmacoinvasive strategy as defined in the included studies, this would suggest the potential for one (range 0 to 3) additional stroke per annum compared with treatment with primary PCI. However, caution is required when inferring a NNTH. None of the RCTs or observational studies were undertaken in Ireland, raising questions regarding the applicability of the data to the Irish healthcare setting. However, it is noted that the trial protocols for the interventions included in this review are reflective of the current model of care in Ireland. The precise impact of a pharmacoinvasive approach on ICH and bleeding outcomes is not known; however, evidence suggests that these may occur more commonly in older patients and may be dose-related.[332]

The approach of an optimal reperfusion strategy that includes both primary PCI and a pharmacoinvasive strategy where appropriate is consistent with that adopted in other jurisdictions. Recent Canadian guidelines recommend that each hospital in a STEMI network has a preplanned default reperfusion strategy that is based on geographical and logistical considerations and can expedite travel to the nearest PCI-capable centre in the case of failed fibrinolysis.[212] Although the pharmacoinvasive strategy may be associated with some safety concerns, ongoing research to identify solutions to mitigate these risks may help to inform appropriate care pathways for selected subgroups who experience these complications. Strategies to expedite travel to the nearest PCI-capable centre are also required for patients who have absolute contraindications to fibrinolytic therapy.

There may be concerns regarding the sustainability of a low-volume PCI centre given that a number of international guidelines specifically recommend that primary PCI

centres should provide a 24/7 service and that they should have a second cath lab on-site. Although part-time PCI centres (that is, PCI centres that only operated for a limited period of time, usually 9am to 5pm Monday to Friday) were identified,[45, 48-54, 93, 100, 108, 113, 116, 120, 121, 123, 124, 128, 146, 167] these tended to be in the minority. As described in RQ2, a number of guidance documents specifically recommended part-time PCI centres only in the context of new PCI centres and only in the first few years of service. Consideration may be given to having PCI operators and other cath lab staff on a rotating roster between high- and low-volume PCI centres within a regional area, which may mitigate some, but not all, of the safety concerns and to ensure 24/7 coverage. While there was heterogeneity between guidelines and networks identified in this review, there are likely minimum infrastructure and staffing requirements to provide safe and sustainable 24/7 services at PCI centres that will pertain irrespective of the volume of procedures provided.[369] Alternatives to investing in new low-volume PCI centres include consideration of the other steps in the pathway from symptom onset to reperfusion such as additional resourcing of prehospital systems of care and or improved interhospital transfer to address specific issues in geographically remote regions. The goal is to maximise patient outcomes while ensuring an efficient or sustainable use of resources; however, a determination of the economic implications of alternative approaches was beyond the scope of this project.

Although there was limited international evidence regarding the structure and organisation of networks for other cardiac conditions, it is plausible that they may fall in line with a 'hub and spoke' model, integrated with STEMI 'hub and spoke' networks. In particular, heart failure networks have been suggested to take a similar structure, however unlike STEMI networks, proposed 'hub and spoke' models for heart failure extend beyond hospital networks into the community.[23, 197, 211] For heart failure networks there would appear to be a greater role for primary care, in particular for patients with stable, low-risk disease, and hence close linkage with general practices and other primary care clinical disciplines, which will be organised within Community Healthcare Organisations may be warranted for service development regionally and nationally. A similar service model may be suitable for cardiac arrhythmia networks, although there was limited evidence to support any particular formation. With regard to adult congenital heart disease (ACHD), it is unclear whether every STEMI network would require a specialist ACHD 'hub' or whether this should be provided at a national level. For example, in Sweden, which has a population of over 10 million inhabitants, there are only two ACHD centres of excellence for the whole country, one of which takes referrals from Iceland.[141] It is important to note that the establishment of any new specialist cardiac network would likely be integrated across the different cardiac conditions to ensure efficiencies of expertise, staffing and equipment.

International guidance documents for PCI service provision were collated and quality appraised in RQ2. Essentially this review question described international best practice for the 'hub' PCI centre. Although there was general consensus in certain areas such as institutional facility requirements and the need for monitoring of standards, there was variation in other areas such as staffing recommendations and minimum volume thresholds. For example, with regard to minimum institutional and operator volumes for PCI procedures, these varied substantially with US guidelines advocating lower volumes than UK guidelines (200 vs. 400 total PCI procedures per institution, 50 vs. 75 total PCI procedures per operator).[11, 178, 262, 268] The pan-European ESC/EACTS guidelines recommend a minimum institutional threshold of 200 procedures for PCI for stable coronary artery disease; however they recommend that facilities providing fewer than 400 procedures per annum should collaborate in networks with higher volume (>400 PCI per year) institutions with exchange of operators and support staff between sites and use of shared written protocols. Moreover, they recommend that primary PCI procedures should only be undertaken in institutions performing at least 400 PCIs per year. The lower volumes advocated in the US guidelines would tend to reflect the relatively smaller populations served by ACS-related networks in the US, and hence the lower procedural volumes produced per centre and reflects the somewhat fragmented nature of US healthcare delivery which is not based on geographical populations.[290, 292] Conversely, ACS-related networks in the UK, generally served much larger geographically based populations, and hence produced higher procedural volumes per centre.[271, 303] Therefore it would follow that care may be needed when using international guidelines to guide service provision, as the recommendations may be context specific and not applicable to the local population. Moreover, the evidence underpinning many of the recommendations of included guidance documents was determined to be weak and the methodology used to develop these recommendations was often unclear, underlining the need to conduct RQ3.

Certain guidelines, in particular the US guidance documents, discussed the limitations of the volume-outcome evidence and cautioned against the preoccupation with specific volume thresholds.[11, 267] As these thresholds are generally arbitrary, context-specific and based on questionable evidence, perhaps more useful for the Irish healthcare system going forward, would be the recommendations regarding the recording and monitoring of KPIs. KPIs are essential tools in monitoring the performance of healthcare services, providing reliable information about current and desired standards, and are critical as a tool for improving the quality of care delivered to a population.[183] Continuous performance monitoring at a hospital-, network-, regional- and national-level using KPIs may provide more useful data to the Irish context than relying on international literature. The UK is an example of one country which undertakes a continuous audit of all PCI procedures conducted in

all public hospitals, and most private hospitals.[191] The audit provides annual information on service provision of PCI services across the UK, appropriateness of clinical care and treatment, process measures and patient outcomes.[192] Continued use of the Irish ACS monitoring system (the Heartbeat portal)[177] and development or expansion of this system to include performance measures for other aspects of specialist cardiac care would provide ongoing critical information about the performance of the system.

International guidance documents generally recommend the monitoring of KPIs such as mortality, time-to-treatment and morbidity/complication rates with a quality assurance programme in place.[12, 175, 178, 260, 261, 263, 264, 266] These KPIs have been monitored across the majority of identified cardiac networks. In the case of PCI networks, although PCI volume has been considered a key quality metric and a useful tool for benchmarking, it has been noted that it should not be used as the sole surrogate for quality of care given that the volume-outcome relationship would appear to be attenuating with time, along with the 'very low' certainty surrounding the evidence overall.[13, 275, 278] Rather it is recommended that PCI volume should be monitored along with a suite of other metrics including procedural (for example, radial access, mortality or complications), post-procedural (for example, medication on discharge, referral to cardiac rehabilitation) and general operator/hospital traits (for example, volume of high-risk sub-populations, appropriate case selection or maintenance of competency).[13] Nevertheless, while there is debate regarding the value of a set minimum volume threshold,[13, 275] guideline organisations that have previously withdrawn set threshold recommendations in relation to volume outcomes later reinstated these recommendations.[268] While the exact reasons for the withdrawal and subsequent restoration of these recommendations are not known, the reinstatement of these thresholds would suggest that guideline organisations consider there to be some value in adhering to minimum volume thresholds.

The findings of our systematic review and meta-analysis conducted in RQ3, indicate that a volume-outcome relationship may still exist in favour of high-volume operators and high-volume primary PCI hospitals, however no significant association was found between total PCI hospital volume and mortality. A temporal trend was observed indicating that the volume-outcome relationship may be attenuating over time. It was not possible to calculate a minimum volume threshold. Given the considerable level of heterogeneity between studies, the review findings need to be understood within the specific context of each study. In Ireland, the 2016 data from the Heartbeat portal found that the number of annual primary PCI procedures conducted across all six designated primary PCI centres ranged from 65 to 320 annual primary PCI procedures.[177] When compared with the seven studies included in this systematic review which examined the volume-outcome relationship for primary PCI at the hospital-level,[294-296, 300, 301, 303, 305] none of the six Irish

designated primary PCI centres would be classified as low-volume, except marginally, in one study where a threshold of 66 primary PCI procedures was used to define low-volume.[305] With regards to total PCI volumes, low-volume definitions among included studies, ranged from 149 PCI procedures per year[299] to 542 PCI procedures per year.[290] Based on Irish Hospital In-Patient Enquiry (HIPE) data for 2017, where the number of PCI procedures conducted in the six designated primary PCI centres in Ireland ranged from 603 to 1,603 total PCI procedures per year, none of these hospitals would be defined as low-volume based on the definitions used among included studies.[174] Hence outcomes from low-volume hospitals as defined by the included studies may not be relevant to the Irish setting. No national data regarding Irish operator volumes were identified.

As highlighted in the previous chapters, a rigorous systematic approach was undertaken throughout this evidence review. Furthermore, the assistance of a steering group with contextual knowledge and strong experience of performing and managing PCI added important clinical insights to this evidence review. Hence the key strength of this evidence review is its robustness leading to findings that are strongly rooted in the evidence, relevant and important for informing national health policy. The main limitation of this evidence review is that many of the included studies had methodological issues and or were observational in nature. Furthermore, the overall certainty of evidence was 'low' or 'very low' in the two review questions where GRADE was applied. It is important that policy makers are aware of the limitations of the evidence base. Questions not prioritised for consideration in this evidence review included a review of the clinical and cost-effectiveness of specialist cardiac networks. Early scoping of this topic by the review team suggested that there may be a limited number of studies which have thoroughly evaluated the effectiveness of such networks. A systematic review published in 2016 by Brown et al. was identified that examined the effectiveness of clinical networks.[6] It found that although the best available evidence indicates that clinical networks can be effective vehicles for quality improvement, the networks were heterogeneous in design and the studies were often of low quality. It noted that many of the quality improvements were incremental and that complex changes and ultimately improvements in patient outcomes were more challenging to evaluate. Findings from qualitative studies in this review suggested that effective networks were those that had adequate resources, credible leadership and efficient management along with effective communication strategies and collaborative trusting relationships. A series of de novo systematic reviews were undertaken to inform recent Canadian guidelines on the acute management of STEMI, focussing on reperfusion and the regionalisation of care.[212] Based on the evidence from the reviews, the guidelines recommend the development of regional STEMI centres ('hub and spoke' model) and concluded that the delivery of timely and appropriate reperfusion therapy is best

delivered within an organised network of STEMI care that incorporates differences in local and regional resources, staff expertise and geographical considerations.

The systematic review by Brown et al. found very limited evidence surrounding the economic impact of the implementation of clinical networks, hence it is unlikely that there is currently sufficient economic evidence to inform development of the most cost-effective model of specialist cardiac care in Ireland.[6]

Of the cost-effectiveness studies identified during the course of this current review, most reported cardiac networks to be cost-effective.[52, 79, 369] One analysis focused on identifying the 'tipping point' when it became efficient to establish a new PCI centre versus the cost of air transport based on population and distance from an existing centre, in a rural region in Canada.[369] Given differences in the structure and funding of healthcare between countries and the known heterogeneity of clinical networks, it is unlikely that international evidence of cost-effectiveness would be directly relevant to the Irish healthcare system. A de-novo economic model would be required to determine the cost-effectiveness in the context of the the Irish healthcare system.

As part of RQ1, we narratively reported the authors' findings regarding temporal changes in networks, and in general, we found that the authors found improvement in efficiencies of care, though the impact on clinical outcomes was less apparent. Many of the findings related to year-on-year improvements within the context of a specialist cardiac network, rather than improvements arising from the implementation of a network. Furthermore caution is required when interpreting these findings as these studies were not subject to the same level of scrutiny as would occur in a systematic review.

Although relevant studies may have been published since the systematic review by Brown et al. was conducted in 2014,[370] the overall findings of this current evidence review are unlikely to have changed had we addressed this question. Furthermore, since international guidelines have strongly recommended that cardiac care be regionalised, [12, 212] healthcare systems are likely to move in this direction regardless, and therefore the usefulness of a systematic review may be questionable. Internationally, specialist services appear to be moving towards networked provision of care.[4, 56, 57, 188] For example in Ireland, disease-specific networks have been established in the areas of end-stage kidney disease,[371] while referral networks have been implemented for patients with severe aortic stenosis requiring transcatheter aortic valve implantation (TAVI).[372] HIQA has published a HTA on the clinical and cost-effectiveness and budget impact of TAVI compared with surgical aortic valve replacement (SAVR) in patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications in Ireland. The

recommendations arising from this HTA are likely to inform the organisation of cardiac care in this cohort. In light of other potential changes to specialist cardiac care in Ireland, such as the aforementioned extension of the national TAVI pathway, along with other national strategies and policies, strategic coherence in the organisation of care is critical.

Another important research question which could have been addressed related to the barriers and facilitators to the implementation of specialist cardiac networks. Such a qualitative evidence synthesis may have provided the Steering Group with useful information from an international perspective regarding how best to implement networks and what challenges exist.

In the event that a specialist adult cardiac network is established that provides care across the range of cardiac conditions identified in Section 1.2, international best practice would suggest that there should be systems for monitoring performance put in place. These data are paramount for health professionals, policy-makers and researchers alike as a means of monitoring the performance of these networks as they develop over time, and for identifying areas for quality improvement. Having data that are reliable and specific to the Irish setting would enable better decision making, and would increase understanding of how best to configure our services rather than relying on international data which will inevitably have caveats.

Recommendations from RQ2 generally agreed that it was advisable to:

(i) invest in a mechanism to allow for the identification and collection of KPI relevant data at regional level

(ii) make it part of the culture to collect and share this KPI data and

(iii) allow for national comparisons and benchmarking as well as a feedback process to allow for improvements.

These general recommendations could be applied to other cardiac networks and services beyond PCI and have been recommended in guidelines from other countries.[373] Cardiovascular registries are present in the US health system and monitor performance across cardiac conditions such as STEMI, atrial fibrillation and congenital heart disease.[374] Continued development of minimum data sets and KPIs, a uniform database across centres and a national prospective registry with an associated quality assurance programme[183] are therefore important next steps in the establishment of high quality, safe, reliable and integrated specialist cardiac networks in Ireland.

When recommending the optimal configuration for specialist cardiac services in

Ireland, consideration should be given to other national strategies and policies and in particular any requirements for common support services. Investment in systems for monitoring performance would be an essential part of the implementation plan. Any quality assurance programme for a cardiac network should allow for the identification and collection of appropriate regional data, benchmarking against agreed national standards, and a feedback mechanism that would allow for improvements in practice.

7 Summary of key outcomes from evidence reviews

International specialist cardiac networks and in particular STEMI networks, were generally found to be organised as 'hub and spoke' models, with more specialised services centralised to high-volume 'hubs', with referring 'spoke' hospitals on the periphery of the system and supported by a coordinated EMS system. Less international evidence was found to support any specific organisation of heart failure, cardiac arrhythmia or ACHD networks though these are likely to integrate with STEMI networks, with greater primary care links in particular for heart failure and cardiac arrhythmia networks. Clear governance structures also appeared to be important for sustainability and development of specialist cardiac networks.

The organisation and service specifications for PCI centres, as the 'hub' of the cardiac network, were systematically collated and the underpinning evidence examined. Although there were common themes that a number of guidance documents agreed on, there were also some clear areas of divergence, which may be related to the differences in healthcare systems of the various countries and regions. Minimum volume threshold recommendations in particular, were quite variable and of uncertain evidence. Moreover, for the majority of included guidance documents, the evidence base underpinning the recommendations and the methodology for formulating the recommendations was unclear. However continuous monitoring of standards was recommended by most guidance documents to ensure safe, effective and high quality care.

The volume-outcome relationship was examined to determine whether high-volume PCI hospitals or operators were associated with better patient outcomes compared to low-volume PCI hospitals or operators, in light of significant advances in interventional cardiology. The systematic review and meta-analysis determined that there was no significant association between total PCI hospital volume and mortality. However, this volume-outcome relationship may still exist in favour of high-volume hospitals for primary PCI procedures and high-volume operators for all PCI indications, although these findings are based on 'very low' certainty evidence and the relationship would appear to be attenuating with time. The evidence is limited due to the considerable levels of heterogeneity, concerns regarding the risk of bias of included studies and variations in definitions of high and low volume for hospitals and operators, and the review results on the volume-outcome relationship should be viewed with caution. Furthermore it was not possible to determine with any degree of certainty a specific minimum volume threshold.

Low- to very low-certainty evidence suggests that for patients whose symptom onset does not exceed 12 hours, a pharmacoinvasive approach may be a suitable alternative to primary PCI for STEMI patients who are unable to access PCI in a

timely manner. Furthermore, evidence suggests that within this context (that is, restricted to patients with initial expected delays in accessing PCI), timely treatment with a pharmacoinvasive strategy may be more effective than delayed primary PCI where the time difference exceeds 80 minutes. This evidence, which is based on literature published since 2008 and should therefore reflect contemporary cardiac care, supports the current optimal reperfusion service (ORS) protocol for Ireland. While there are some safety concerns with regards minor bleeding (which is driving total bleeding events) and ICH (which is driving total stroke events), these adverse events are uncommon. Implementation of appropriate care pathways for patients who experience these complications, including use of alternative dosing strategies in older patients, may mitigate these risks.

When configuring specialist cardiac services in Ireland, consideration should be given to other national strategies and policies and in particular any requirements for common support services. Investment in systems for monitoring performance would be an essential part of the implementation plan. Any quality assurance programme for a cardiac network should allow for the identification and collection of appropriate regional data, benchmarking against agreed national standards, and a feedback mechanism that would allow for improvements in practice.

References

1. Department of Health. National Review of Specialist Cardiac Services 2018 [Available from: https://health.gov.ie/national-patient-safety-office/ncec/clinical-practice-guidance/national-review-of-specialist-cardiac-services/.
2. Gauss T, Balandraud P, Frandon J, Abba J, Ageron FX, Albaladejo P, et al. Strategic proposal for a national trauma system in France. Anaesthesia Critical Care & Pain Medicine. 2018.
3. Department of Health. A Trauma System for Ireland: Report of the Trauma Steering Group. Dublin: Department of Health, 2018.
4. Hunter RM, Davie C, Rudd A, Thompson A, Walker H, Thomson N, et al. Impact on clinical and cost outcomes of a centralized approach to acute stroke care in London: a comparative effectiveness before and after model. PloS one. 2013;8(8):e70420.
5. Health Service Executive Quality and Clinical Care Directorate. Stroke Clinical Care Programme: Model of Care. 2012.
6. Brown BB, Patel C, McInnes E, Mays N, Young J, Haines M. The effectiveness of clinical networks in improving quality of care and patient outcomes: a systematic review of quantitative and qualitative studies. BMC health services research. 2016;16(1):360.
7. Morche J, Mathes T, Pieper D. Relationship between surgeon volume and outcomes: a systematic review of systematic reviews. Systematic reviews. 2016;5(1):204.
8. Lin X, Tao H, Cai M, Liao A, Cheng Z, Lin H. A systematic review and meta-analysis of the relationship between hospital volume and the outcomes of percutaneous coronary intervention. Medicine. 2016;95(5).
9. Post PN, Kuijpers M, Ebels T, Zijlstra F. The relation between volume and outcome of coronary interventions: a systematic review and meta-analysis. Eur Heart J. 2010;31(16):1985-92.
10. Strom JB, Wimmer NJ, Wasfy JH, Kennedy K, Yeh RW. Association between operator procedure volume and patient outcomes in percutaneous coronary intervention: a systematic review and meta-analysis. Circulation: Cardiovascular Quality and Outcomes. 2014;7(4):560-6.
11. Harold JG, Bass TA, Bashore TM, Brindis RG, Brush JE, Burke JA, et al. ACCF/AHA/SCAI 2013 update of the clinical competence statement on coronary artery interventional procedures: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training (writing committee to revise the 2007 clinical competence statement on cardiac interventional procedures). Journal of the American College of Cardiology. 2013;62(4):357-96.
12. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2019;40(2):87-165.
13. Kumbhani D, Nallamothu B. PCI Volume Benchmarks: Still Adequate for Quality Assessment in 2017? Journal of the American College of Cardiology. 2017;69(24):2925.
14. Avdic D. Improving efficiency or impairing access? Health care consolidation and quality of care: Evidence from emergency hospital closures in Sweden. Journal of health economics. 2016;48:44-60.
15. Goodwin N, Peck E, Freeman T, Posaner R. Managing across diverse networks of care: lessons from other sectors. Report to the NHS SDO R&D Programme Birmingham: Health Services Management Centre, University of Birmingham. 2004.
16. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Medical Research Methodology. 2018;18(1):143.
17. Peterson J, Pearce PF, Ferguson LA, Langford CA. Understanding scoping reviews: Definition, purpose, and process. Journal of the American Association of Nurse Practitioners. 2017;29(1):12-6.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9.
19. Tricco AC, Lillie E, Zarin W, et al. Prisma extension for scoping reviews (prisma-scr): Checklist and explanation. Annals of Internal Medicine. 2018;169(7):467-73.

20. Adapte Collaboration. The ADAPTE process: resource toolkit for guideline adaptation. Version 2.0. 2009 2009 [Available from: https://www.g-i-n.net/document-store/working-groups-documents/adaptation/adapte-resource-toolkit-guideline-adaptation-2-0.pdf.
21. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Jama. 2000;283(15):2008-12.
22. Health Informationand Quality Authority. Evidence synthesis process; Methods in the development of National Standards, Guidance and Recommendations for the Irish health and social care sector. 2018.
23. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. European journal of heart failure. 2018;20(11):1505-35.
24. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European journal of cardio-thoracic surgery. 2016;50(5):e1-e88.
25. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31(23):2915-57.
26. Bagai A, Al-Khalidi HR, Sherwood MW, Munoz D, Roettig ML, Jollis JG, et al. Regional systems of care demonstration project: Mission: Lifeline STEMI Systems Accelerator: design and methodology. Am Heart J. 2014;167(1):15-21.e3.
27. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet (London, England). 2003;361(9351):13-20.
28. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. The New England journal of medicine. 2003;349(8):733-42.
29. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. Circulation. 2003;108(15):1809-14.
30. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial--PRAGUE-2. Eur Heart J. 2003;24(1):94-104.
31. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. European heart journal. 2003;24(1):28-66.
32. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109(10):1223-5.
33. Elrod JK, Fortenberry JL. The hub-and-spoke organization design: an avenue for serving patients well. BMC Health Services Research. 2017;17(1):457.
34. Colquhoun HL, Levac D, O'Brien KK, Straus S, Tricco AC, Perrier L, et al. Scoping reviews: time for clarity in definition, methods, and reporting. Journal of clinical epidemiology. 2014;67(12):1291-4.
35. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International journal of social research methodology. 2005;8(1):19-32.
36. United Nations Development Programme. Global Human Development Indicators http://hdr.undp.org/en/countries2018 [
37. European Union (EU). Countries of the EU 2019 [Available from: https://europa.eu/european-union/about-eu/countries_en#tab-0-1.
38. Campo G, Menozzi M, Guastaroba P, Vignali L, Belotti LM, Casella G, et al. Same-day transfer for the invasive strategy of patients with non-ST-segment elevation acute coronary syndrome admitted to spoke hospitals: Data from the Emilia-Romagna Regional Network. Eur Heart J Acute Cardiovasc Care. 2016;5(6):428-34.
39. Casella G, Ottani F, Ortolani P, Guastaroba P, Santarelli A, Balducelli M, et al. Off-hour primary percutaneous coronary angioplasty does not affect outcome of patients with ST-Segment elevation acute myocardial infarction treated within a regional network for

reperfusion: The REAL (Registro Regionale Angioplastiche dell'Emilia-Romagna) registry. JACC Cardiovasc Interv. 2011;4(3):270-8.

40. Manari A, Ortolani P, Guastaroba P, Casella G, Vignali L, Varani E, et al. Clinical impact of an inter-hospital transfer strategy in patients with ST-elevation myocardial infarction undergoing primary angioplasty: the Emilia-Romagna ST-segment elevation acute myocardial infarction network. Eur Heart J. 2008;29(15):1834-42.
41. Ortolani P, Marzocchi A, Marrozzini C, Palmerini T, Saia F, Taglieri N, et al. Pre-hospital ECG in patients undergoing primary percutaneous interventions within an integrated system of care: reperfusion times and long-term survival benefits. EuroIntervention. 2011;7(4):449-57.
42. Pavesi PC, Guastaroba P, Casella G, Berti E, De Palma R, Di Bartolomeo S, et al. [Quality indicators for the assessment of ST-segment elevation acute myocardial infarction (STEMI) networks. How hospital discharge records could be integrated with Emergency medical services data: the Emilia-Romagna STEMI network experience]. G Ital Cardiol (Rome). 2015;16(9):501-7.
43. Pavesi PC, Nobilio L, De Palma R, Casella G, Di Pasquale G, Grilli R. [The evolution of intensive cardiac care units and the effects of interhospital networks for reperfusion implementation. Analysis of the Emilia-Romagna regional data, 2002 to 2007]. G Ital Cardiol (Rome). 2011;12(1):31-42.
44. Perugini E, Di Diodoro L, Ortolani P, Casella G, Sangiorgio P, Marzocchi A, et al. What is the acceptable rate of false positives for STEMI within a primary PCI hub & spoke network? Eur Heart J. 2010;31:484.
45. Radke PW, Halvorsen S, Jukema JW, Kolh P, Annemans L, Postma MJ, et al. Networks for improving care in patients with acute coronary syndrome: A framework. Acute Card Care. 2014;16(2):41-8.
46. Saia F, Marrozzini C, Ortolani P, Palmerini T, Guastaroba P, Cortesi P, et al. Optimisation of therapeutic strategies for ST-segment elevation acute myocardial infarction: the impact of a territorial network on reperfusion therapy and mortality. Heart. 2009;95(5):370-6.
47. Taglieri N, Saia F, Lanzillotti V, Marrozzini, Faccioli R, Iarussi B, et al. Impact of a territorial ST-segment elevation myocardial infarction network on prognosis of patients with out-of-hospital cardiac arrest. Acute Card Care. 2011;13(3):143-7.
48. Bosch X, Curós A, Argimon JM, Faixedas M, Figueras J, Xavier Jiménez Fàbrega F, et al. The Primary Percutaneous Coronary Intervention Program in Catalonia. Revista Espanola de Cardiologia Suplementos. 2011;11(SUPPL. 3):51-60.
49. Fernandez-Rodriguez D, Freixa X, Kasa G, Regueiro A, Cevallos J, Hernandez M, et al. [Benefit of the implementation of a ST-segment elevation myocardial infarction network on women]. Arch Cardiol Mex. 2015;85(2):96-104.
50. Fernandez-Rodriguez D, Regueiro A, Cevallos J, Bosch X, Freixa X, Trilla M, et al. Gender gap in medical care in ST segment elevation myocardial infarction networks: Findings from the Catalan network Codi Infart. Med Intensiva. 2017;41(2):70-7.
51. Garcia-Garcia C, Ribas N, Recasens LL, Merono O, Subirana I, Fernandez A, et al. In-hospital prognosis and long-term mortality of STEMI in a reperfusion network. "Head to head" analisys: invasive reperfusion vs optimal medical therapy. BMC Cardiovasc Disord. 2017;17(1):139.
52. Regueiro A, Bosch J, Martin-Yuste V, Rosas A, Faixedas MT, Gomez-Hospital JA, et al. Cost-effectiveness of a European ST-segment elevation myocardial infarction network: results from the Catalan Codi Infart network. BMJ Open. 2015;5(12):e009148.
53. Regueiro A, Fernandez-Rodriguez D, Freixa X, Bosch X, Martin-Yuste V, Brugaletta S, et al. False Positive STEMI Activations in a Regional Network: Comprehensive Analysis and Clinical Impact. Results From the Catalonian Codi Infart Network. Rev Esp Cardiol (Engl Ed). 2018;71(4):243-9.
54. Regueiro A, Tresserras R, Goicolea J, Fernández-Ortiz A, Macaya C, Sabaté M. Primary percutaneous coronary intervention: models of intervention in Spain. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2012;8:P90-3.
55. Eurostat. Gross domestic product (GDP) at current market prices by NUTS 2 regions http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=nama_10r_2gdp&lang=en2019 [
56. NHS England. The Way Forward: Strategic Clinical Networks: NHS England; 2012 [Available

from: https://www.england.nhs.uk/wp-content/uploads/2012/07/way-forward-scn.pdf.

57. Rhudy Jr JP, Bakitas MA, Hyrkäs K, Jablonski-Jaudon RA, Pryor ER, Wang HE, et al. Effectiveness of regionalized systems for stroke and myocardial infarction. Brain and behavior. 2015;5(10):e00398.
58. National Health Service. NHS structure explained https://www.nhs.uk/using-the-nhs/about-the-nhs/nhs-structure-explained/2016 [
59. The Commonwealth Fund. The Italian Health Care System https://international.commonwealthfund.org/countries/italy/2019 [
60. The Commonwealth Fund. The English Health Care System https://international.commonwealthfund.org/countries/england/2019 [
61. World Health Organization. Catalonia, Spain. http://www.euro.who.int/__data/assets/pdf_file/0004/373387/rhn-catalonia-eng.pdf?ua=12018 [
62. Instituto Nazionale di Statistica. Demographic Indicators: Estimates for the year 2018 https://www.istat.it/it/files//2019/02/Indicatoridemografici2018_EN.pdf2019 [
63. Office for National Statistics. Population estimates https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates2019 [
64. Statistical Institute of Catalonia. Population of Catalonia https://www.idescat.cat/indicadors/?id=anuals&n=10328&col=1&lang=en2019 [
65. European Commission. Factsheet on 2014-2020 Rural Development Programme for Emilia-Romagna https://ec.europa.eu/agriculture/sites/agriculture/files/rural-development-2014-2020/country-files/it/factsheet-emilia-romagna_en.pdf2014 [
66. European Commission. Factsheet on 2014-2020 Rural Development Programme for Cataluna https://enrd.ec.europa.eu/sites/enrd/files/es_cat_rdp_qnt_summary_v1.pdf2015 [
67. Eurostat. GDP per capita in 281 EU regions https://ec.europa.eu/eurostat/documents/2995521/9618249/1-26022019-AP-EN.pdf/f765d183-c3d2-4e2f-9256-cc6665909c802019 [
68. Adam WH, Yuvaraj M, Ian J, Bill B, Edward W, George B, et al. Prehospital 12-Lead ECG to Triage ST-Elevation Myocardial Infarction and Emergency Department Activation of the Infarct Team Significantly Improves Door-to-Balloon Times. Circulation: cardiovascular interventions. 2009;2(6):528-34.
69. Agarwal AK, Gaieski DF, Perman SM, Leary M, Delfin G, Abella BS, et al. Telemedicine REsuscitation and Arrest Trial (TREAT): A feasibility study of real-time provider-to-provider telemedicine for the care of critically ill patients. Heliyon 2016;2:e00099.
70. Aguirre FV, Varghese JJ, Kelley MP, Lam W, Lucore CL, Gill JB, et al. Rural interhospital transfer of ST-elevation myocardial infarction patients for percutaneous coronary revascularization: the Stat Heart Program. Circulation. 2008;117(9):1145-52.
71. Antoni ML, Hoogslag GE, Boden H, Liem SS, Boersma E, Fox K, et al. Cardiovascular mortality and heart failure risk score for patients after ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention (Data from the Leiden MISSION! Infarct Registry). Am J Cardiol. 2012;109(2):187-94.
72. Aplin R, Tiede D, Lovitz C, Gartner M, Robinson D, Xu H, et al. A regional system for delivery of primary percutaneous coronary intervention in ST-elevation myocardial infarction: STEMI-St. Cloud. J Invasive Cardiol. 2009;21(12):639-44.
73. Assyag P, Renaud T, Cohen-Solal A, Viaud M, Krys H, Bundalo A, et al. RESICARD: East Paris network for the management of heart failure: absence of effect on mortality and rehospitalization in patients with severe heart failure admitted following severe decompensation. Arch Cardiovasc Dis. 2009;102(1):29-41.
74. Atary JZ, de Visser M, van den Dijk R, Bosch J, Liem SS, Antoni ML, et al. Standardised pre-hospital care of acute myocardial infarction patients: MISSION! guidelines applied in practice. Netherlands Heart Journal. 2010;18(9):408-15.
75. Atary JZ, van der Hoeven BL, Liem SS, Jukema JW, van der Bom JG, Atsma DE, et al. Three-Year Outcome of Sirolimus-Eluting Versus Bare-Metal Stents for the Treatment of ST-Segment Elevation Myocardial Infarction (from the MISSION! Intervention Study). Am J Cardiol. 2010;106(1):4-12.
76. Babić Z, Pintarić H, Starcević B, Bulum J, Tomulić V, Giunio L, et al. Seven-year trends in the

croatian primary percutaneous coronary intervention network. Acta Clin Croat. 2015;54(3):351-8.

77. Bajka B, Orzan M, Jakó B, Kovács I. Distance-related differences in critical times, protocol activation and mortality in a regional STEMI network. Journal of Cardiovascular Emergencies. 2016;2(3):122-8.
78. Benedek I, Gyongyosi M, Benedek T. A prospective regional registry of ST-elevation myocardial infarction in Central Romania: impact of the Stent for Life Initiative recommendations on patient outcomes. Am Heart J. 2013;166(3):457-65.
79. Birkemeyer R, Dauch A, Müller A, Beck M, Schneider H, Ince H, et al. Short term cost effectiveness of a regional myocardial infarction network. Health Econ Rev. 2013;3(1):1-8.
80. Birkemeyer R, Rillig A, Koch A, Miljak T, Kunze M, Meyerfeldt U, et al. Primary angioplasty for any patient with ST-elevation myocardial infarction? Guideline-adherent feasibility and impact on mortality in a rural infarction network. Clinical research in cardiology. 2010;99(12):833-40.
81. Boden H, van der Hoeven BL, Liem SS, Atary JZ, Cannegieter SC, Atsma DE, et al. Five-year clinical follow-up from the MISSION! Intervention Study: sirolimus-eluting stent versus bare metal stent implantation in patients with ST-segment elevation myocardial infarction, a randomised controlled trial. EuroIntervention. 2012;7(9):1021-9.
82. Bosson N, Kaji AH, Niemann JT, Eckstein M, Rashi P, Tadeo R, et al. Survival and neurologic outcome after out-of-hospital cardiac arrest: results one year after regionalization of post-cardiac arrest care in a large metropolitan area. Prehosp Emerg Care. 2014;18(2):217-23.
83. Brooks SC, Scales DC, Pinto R, Dainty KN, Racz EM, Gaudio M, et al. The Postcardiac Arrest Consult Team: Impact on Hospital Care Processes for Out-of-Hospital Cardiac Arrest Patients. Crit Care Med. 2016;44(11):2037-44.
84. Bruder O, Breuckmann F, Jensen C, Jochims M, Naber CK, Barkhausen J, et al. Prognostic impact of contrast-enhanced CMR early after acute ST segment elevation myocardial infarction (STEMI) in a regional STEMI network. Herz Kardiovaskuläre Erkrankungen. 2008;33(2):136-42.
85. Brunetti ND, De Gennaro L, Dellegrottaglie G, Amoruso D, Antonelli G, Di Biase M. A regional prehospital electrocardiogram network with a single telecardiology "hub" for public emergency medical service: technical requirements, logistics, manpower, and preliminary results. Telemed J E Health. 2011;17(9):727-33.
86. Brunetti ND, De Gennaro L, Dellegrottaglie G, Di Giuseppe G, Antonelli G, Di Biase M. All for one, one for all: Remote telemedicine hub pre-hospital triage for public Emergency Medical Service 1-1-8 in a regional network for primary PCI in Apulia, Italy. European Research in Telemedicine. 2014;3(1):9-15.
87. Buchholz J, Naber CK, Budde T, Koslowski B, Hailer B, Jacksch R, et al. [STEMI network Essen-in-hospital results]. Herz. 2008;33(2):148-52.
88. Chacornac M, Baronne-Rochette G, Schmidt MH, Savary D, Habold D, Bouvaist H, et al. Characteristics and management of acute ST-segment elevation myocardial infarctions occurring in ski resorts in the French Alps: Impact of an acute coronary care network. Arch Cardiovasc Dis. 2010;103(8-9):460-8.
89. Chan AW, Kornder J, Elliott H, Brown RI, Dorval JF, Charania J, et al. Improved survival associated with pre-hospital triage strategy in a large regional ST-segment elevation myocardial infarction program. JACC Cardiovasc Interv. 2012;5(12):1239-46.
90. Claeys MJ, Sinnaeve PR, Convens C, Dubois P, Boland J, Vranckx P, et al. STEMI mortality in community hospitals versus PCI-capable hospitals: results from a nationwide STEMI network programme. Eur Heart J Acute Cardiovasc Care. 2012;1(1):40-7.
91. Clemmensen P, Schoos MM, Lindholm MG, Rasmussen LS, Steinmetz J, Hesselfeldt R, et al. Pre-hospital diagnosis and transfer of patients with acute myocardial infarction--a decade long experience from one of Europe's largest STEMI networks. J Electrocardiol. 2013;46(6):546-52.
92. Dalby M, Kharbanda R, Ghimire G, Spiro J, Moore P, Roughton M, et al. Achieving routine sub 30 minute door-to-balloon times in a high volume 24/7 primary angioplasty center with autonomous ambulance diagnosis and immediate catheter laboratory access. Am Heart J. 2009;158(5):829-35.
93. DelliFraine J, Langabeer J, 2nd, Segrest W, Fowler R, King R, Moyer P, et al. Developing an ST-elevation myocardial infarction system of care in Dallas County. Am Heart J.

2013;165(6):926-31.

94. Dudek D, Dziewierz A, Siudak Z, Rakowski T, Zalewski J, Legutko J, et al. Transportation with very long transfer delays (>90 min) for facilitated PCI with reduced-dose fibrinolysis in patients with ST-segment elevation myocardial infarction: the Krakow Network. Int J Cardiol. 2010;139(3):218-27.
95. Dudek D, Siudak Z, Dziewierz A, Rakowski T, Mielecki W, Brzezinski M, et al. Local hospital networks for STEMI treatment for a population of half a million inhabitants increase the use of invasive treatment of acute coronary syndromes to the European recommended level. The Malopolska Registry of Acute Coronary Syndromes 2005-2006. Kardiol Pol. 2008;66(5):489-97, discussion 98.
96. Evans LW, van Woerden H, Davies GR, Fone D. Impact of service redesign on the socioeconomic inequity in revascularisation rates for patients with acute myocardial infarction: a natural experiment and electronic record-linked cohort study. BMJ Open. 2016;6(10):e011656.
97. Falsini G, Liistro F, Ducci K, Angioli P, Baldassarre S, Sabini A, et al. Shifting from pharmacological to systematic mechanical reperfusion therapy for acute myocardial infarction via a cooperating network: impact on reperfusion rate and in-hospital mortality. J Cardiovasc Med (Hagerstown). 2008;9(3):245-50.
98. Findlay I, Morris T, Zhang R, McCowan C, Shield S, Forbes B, et al. Linking hospital patient records for suspected or established acute coronary syndrome in a complex secondary care system: a proof-of-concept e-registry in National Health Service Scotland. European heart journal - Quality of Care and Clinical Outcomes. 2018;4(3):155-67.
99. Fordyce CB, Cairns JA, Singer J, Lee T, Park JE, Vandegriend RA, et al. Evolution and Impact of a Regional Reperfusion System for ST-Elevation Myocardial Infarction. Can J Cardiol. 2016;32(10):1222-30.
100. Fordyce CB, Henry TD, Granger CB. Implementation of Regional ST-Segment Elevation Myocardial Infarction Systems of Care: Successes and Challenges. Interv Cardiol Clin. 2016;5(4):415-25.
101. Freixa-Pamias R, Gracia PB, Rodriguez Latre ML, Basile L, Chamero PS, Martinez-Rubio A, et al. Impact of an integral assistance model between primary care and cardiology on the management of patients with ischemic heart disease or atrial fibrillation. J Comp Eff Res. 2019;8(2):103-11.
102. Glickman S, Cairns C, O'Brien S, Ou F, Lytle B, Granger C, et al. The impact of a statewide ST-segment myocardial infarction regionalization program on treatment times for women, minorities, and elderly patients at hospitals without percutaneous coronary intervention capability. Ann Emerg Med. 2009;54(3):S2-S3.
103. Glickman SW, Lytle BL, Ou FS, Mears G, O'Brien S, Cairns CB, et al. Care processes associated with quicker door-in-door-out times for patients with ST-elevation-myocardial infarction requiring transfer: results from a statewide regionalization program. Circ Cardiovasc Qual Outcomes. 2011;4(4):382-8.
104. Gomes V, Brandao V, Mimoso J, Gago P, Trigo J, Santos W, et al. Implementation of a pre-hospital network favoring primary angioplasty in STEMI to reduce mortality: the Algarve Project. Rev Port Cardiol. 2012;31(3):193-201.
105. Grieco N, Sesana G, Corrada E, Ieva F, Paganoni A, Marzegalli M. Mortality and ST resolution in patients admitted with STEMI: the MOMI survey of emergency service experience in a complex urban area. Eur Heart J Acute Cardiovasc Care. 2012;1(3):192-9.
106. Hailer B, Naber C, Koslowski B, van Leeuwen P, Schafer H, Budde T, et al. Gender-related differences in patients with ST-elevation myocardial infarction: results from the registry study of the ST elevation myocardial infarction network Essen. Clin Cardiol. 2011;34(5):294-301.
107. Hailer B, Naber CK, Koslowski B, Budde T, Jacksch R, Sabin G, et al. [STEMI network Essen--results after 1 year]. Herz. 2008;33(2):153-7.
108. Haller PM, Jäger B, Farhan S, Christ G, Schreiber W, Weidinger F, et al. Impact of age on short- and long-term mortality of patients with ST-elevation myocardial infarction in the VIENNA STEMI network. Wien Klin Wochenschr. 2018;130(5-6):172-81.
109. Hassan AK, Liem SS, van der Kley F, Bergheanu SC, Wolterbeek R, Bosch J, et al. In-ambulance abciximab administration in STEMI patients prior to primary PCI is associated with smaller infarct size, improved LV function and lower incidence of heart failure: results from

the Leiden MISSION! acute myocardial infarction treatment optimization program. Catheter Cardiovasc Interv. 2009;74(2):335-43.

110. Heitzler VN, Babic Z, Milicic D, Starcevic B, Mirat J, Strozzi M, et al. Evaluation of importance of door-to-balloon time and total ischemic time in acute myocardial infarction with ST-elevation treated with primary percutaneous coronary intervention. Acta Clin Croat. 2012;51(3):387-95.
111. Henry TD, Sharkey SW, Burke MN, Chavez IJ, Graham KJ, Henry CR, et al. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. Circulation. 2007;116(7):721-8.
112. Herity N, Corrigan D, McNeill A. Transformation of Heart Attack Care: A Primary Percutaneous Coronary Intervention Service for Northern Ireland. Ulster Med J. 2019;88(1):36-40.
113. Huber K, Goldstein P, Danchin N, Fox KA, Welsh R, Granger CB, et al. Enhancing the efficacy of delivering reperfusion therapy: a European and North American experience with ST-segment elevation myocardial infarction networks. Am Heart J. 2013;165(2):123-32.
114. Íñiguez Romo A, Vázquez González N, Trillo Nouche R, Antonio Baz J, Manuel Vázquez J, Castro Beiras A, et al. The Primary Percutaneous Coronary Intervention Program in Galicia. Revista Espanola de Cardiologia Suplementos. 2011;11(SUPPL. 3):44-50.
115. Jacksch R, Naber CK, Koslowski B, Budde T, Hailer B, Sabin G, et al. [Primary Coronary Intervention (PCI) within the myocardial infarction network system in a German city (Essen)]. Herz. 2008;33(2):110-4.
116. Jager B, Farhan S, Kalla K, Glogar HD, Christ G, Karnik R, et al. One-year mortality in patients with acute ST-elevation myocardial infarction in the Vienna STEMI registry. Wien Klin Wochenschr. 2015;127(13-14):535-42.
117. Jollis JG, Mehta RH, Roettig ML, Berger PB, Babb JD, Granger CB. Reperfusion of acute myocardial infarction in North Carolina emergency departments (RACE): study design. Am Heart J. 2006;152(5):851. e1-. e11.
118. Jollis JG, Roettig ML, Aluko AO, Anstrom KJ, Applegate RJ, Babb JD, et al. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. Jama. 2007;298(20):2371-80.
119. Kahlon TS, Barn K, Akram MM, Blankenship JC, Bower-Stout C, Carey DJ, et al. Impact of pre-hospital electrocardiograms on time to treatment and one year outcome in a rural regional ST-segment elevation myocardial infarction network. Catheter Cardiovasc Interv. 2017;89(2):245-51.
120. Kalla K, Christ G, Karnik R, Malzer R, Norman G, Prachar H, et al. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). Circulation. 2006;113(20):2398-405.
121. Knot J, Widimsky P, Wijns W, Stenestrand U, Kristensen SD, Van THA, et al. How to set up an effective national primary angioplasty network: lessons learned from five European countries. EuroIntervention. 2009;5(3):299, 301-9.
122. Labarere J, Belle L, Fourny M, Vanzetto G, Debaty G, Delgado D, et al. Regional system of care for ST-segment elevation myocardial infarction in the Northern Alps: a controlled pre- and postintervention study. Arch Cardiovasc Dis. 2012;105(8-9):414-23.
123. Langabeer JR, 2nd, Champagne-Langabeer T, Helton JR, Segrest W, Kash B, DelliFraine J, et al. Interorganizational Collaboration in Emergency Cardiovascular Care. Qual Manag Health Care. 2017;26(1):1-6.
124. Langabeer JR, 2nd, Henry TD, Fowler R, Champagne-Langabeer T, Kim J, Jacobs AK. Sex-Based Differences in Discharge Disposition and Outcomes for ST-Segment Elevation Myocardial Infarction Patients Within a Regional Network. J Womens Health (Larchmt). 2018;27(8):1001-6.
125. Lapostolle F, Bataille S, Tafflet M, Dupas F, Laborne F, Mouranche X, et al. [Evolution since 2002 of the management of patients with ST elevated acute coronary syndrome (STEMI) in Ile-de-France. E-MUST survey]. Presse Med. 2015;44(7-8):e273-81.
126. Le May MR, So DY, Dionne R, Glover CA, Froeschl MPV, Wells GA, et al. A Citywide Protocol for Primary PCI in ST-Segment Elevation Myocardial Infarction. New England journal of medicine. 2008;358(3):231-40.
127. Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, et al.

MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. Am Heart J. 2007;153(1):14.e1-1.

128. Lin A, Oh T, Alawami M, Webster M, El-Jack S, Scott D, et al. A Review of a Regional Primary Percutaneous Coronary Intervention Service, with a Focus on Door to Reperfusion Times: The 2012 Auckland/Northland Experience. Heart Lung and Circulation. 2015;24(1):11-20.
129. Liverpool Heart and Chest Hospital. CHD Services - Frequently Asked Questions https://www.lhch.nhs.uk/our-services/cardiology/congenital-heart-disease-chd-services/chd-services-frequently-asked-questions/2019 [Available from: https://www.lhch.nhs.uk/our-services/cardiology/congenital-heart-disease-chd-services/chd-services-frequently-asked-questions/.
130. Madison JD, Stokman PJ, Garberich RF, Sharkey SW, Henry TD, Dirks TG, et al. Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. Eur Heart J. 2011;33(10):1232-40.
131. Markus F, Jens H, Hans-Joerg B, Annett S, Sylke S, Martin K, et al. Implementation of Guidelines for the Treatment of Acute ST-Elevation Myocardial Infarction. Circulation: cardiovascular interventions. 2008;1(2):95-102.
132. Mercuri M, Welsford M, Schwalm JD, Mehta SR, Rao-Melacini P, Sheth T, et al. Providing optimal regional care for ST-segment elevation myocardial infarction: a prospective cohort study of patients in the Hamilton Niagara Haldimand Brant Local Health Integration Network. CMAJ Open. 2015;3(1):E1-7.
133. Minha S, Loh JP, Satler LF, Barbash IM, Magalhaes MA, Ben-Dor I, et al. Transfer distance effect on reperfusion: timeline of ST-elevation patients transferred for primary percutaneous coronary intervention. Cardiovascular Revascularization Medicine. 2014;15(8):369-74.
134. Modre-Osprian R, Gruber K, Kreiner K, Schreier G, Poelzl G, Kastner P. Textual analysis of collaboration notes of the telemedical heart failure network HerzMobil Tirol. Stud Health Technol Inform. 2015;212:57-64.
135. Modre-Osprian R, Polzl G, Von Der Heidt A, Kastner P. Closed-loop healthcare monitoring in a collaborative heart failure network. Stud Health Technol Inform. 2014;198:17-24.
136. Mooney MR, Unger BT, Boland LL, Burke MN, Kebed KY, Graham KJ, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. Circulation. 2011;124(2):206-14.
137. Moore MJ, Roberts L, Liew HB, Briganti EM, New G. Transferring patients for primary angioplasty in eastern Melbourne (the SHIPEM registry): are we meeting the guidelines? Med J Aust. 2010;192(12):702-7.
138. Munoz D, Roettig ML, Monk L, Al-Khalidi H, Jollis JG, Granger CB. Transport time and care processes for patients transferred with ST-segment-elevation myocardial infarction: the reperfusion in acute myocardial infarction in Carolina emergency rooms experience. Circ Cardiovasc Interv. 2012;5(4):555-62.
139. Nagayoshi Y, Oshima S, Ogawa H. Clinical Impact of Telemedicine Network System at Rural Hospitals Without On-Site Cardiac Surgery Backup. Telemed J E Health. 2016;22(11):960-4.
140. Heitzler VN, Babic Z, Milicic D, Bergovec M, Raguz M, Mirat J, et al. Results of the Croatian Primary Percutaneous Coronary Intervention Network for patients with ST-segment elevation acute myocardial infarction. American Journal of Cardiology. 2010;105(9):1261-7.
141. Nozohoor S, Gustafsson R, Kallonen J, Sjogren J. Midterm results of surgery for adults with congenital heart disease centralized to a Swedish cardiothoracic center. Congenit Heart Dis. 2013;8(4):273-80.
142. Orzan M, Benedek T, Bajka B, Pál K, Rat N, Benedek I. Impact of a preexisting STEMI network in improving STEMI diagnostic and treatment in the community after the introduction of a national program of interventional treatment in acute myocardial infarction. Journal of Cardiovascular Emergencies. 2015;1(1):23-8.
143. Patterson T, Perkins A, Perkins GD, Clayton T, Evans R, Nguyen H, et al. Rationale and design of: A Randomized tRial of Expedited transfer to a cardiac arrest center for non-ST elevation out-of-hospital cardiac arrest: The ARREST randomized controlled trial. Am Heart J. 2018;204:92-101.
144. Perugini E, Di Pasquale G, Di Diodoro L, Ortolani P, Casella G, Sangiorgio P, et al. What is the acceptable rate of false positives for STEMI within a primary PCI network? Insights from a

metropolitan system with direct ambulance-based access. Int J Cardiol. 2012;154(3):4356-358.

145. Pfister R, Lee S, Kuhr K, Baer F, Fehske W, Hoepp HW, et al. Impact of the Type of First Medical Contact within a Guideline-Conform ST-Elevation Myocardial Infarction Network: A Prospective Observational Registry Study. PLoS One. 2016;11(6):e0156769.
146. Queensland Health. Statewide Cardiac Clinical Network: Queensland Cardiac Outcomes Registry, 2017 Annual Report. Queensland, Australia: Clinical Excellence Division, Queensland Government, 2017.
147. Rathod KS, Koganti S, Iqbal MB, Jain AK, Kalra SS, Astroulakis Z, et al. Contemporary trends in cardiogenic shock: Incidence, intra-aortic balloon pump utilisation and outcomes from the London Heart Attack Group. Eur Heart J Acute Cardiovasc Care. 2018;7(1):16-27.
148. Rokos IC, French WJ, Koenig WJ, Stratton SJ, Nighswonger B, Strunk B, et al. Integration of pre-hospital electrocardiograms and ST-elevation myocardial infarction receiving center (SRC) networks: impact on Door-to-Balloon times across 10 independent regions. JACC Cardiovasc Interv. 2009;2(4):339-46.
149. Saia M, Fonzo M, Pilerci C. The STEMI Network of Veneto Region, Italy. Journal of Medical Practice and Review. 2018;2(07).
150. Saia M, Mantoan D, Fonzo M, Bertoncello C, Soattin M, Sperotto M, et al. Impact of the Regional Network for AMI in the Management of STEMI on Care Processes, Outcomes and Health Inequities in the Veneto Region, Italy. Int J Environ Res Public Health. 2018;15(9).
151. Scholz KH, Hilgers R, Ahlersmann D, Duwald H, Nitsche R, von Knobelsdorff G, et al. Contact-to-balloon time and door-to-balloon time after initiation of a formalized data feedback in patients with acute ST-elevation myocardial infarction. Am J Cardiol. 2008;101(1):46-52.
152. Schoos MM, Pedersen F, Holmvang L, Engstrom T, Saunamaki K, Helqvist S, et al. Optimal catchment area and primary PCI centre volume revisited: a single-centre experience in transition from high-volume centre to "mega centre" for patients with ST-segment elevation myocardial infarction. EuroIntervention. 2015;11(5):503-10.
153. Seiner J, Polasek R, Strejcek M, Karasek J. Cardiac arrest center – One-year experience of the Regional Hospital Liberec. Cor et Vasa. 2018;60(3):e234-e8.
154. Shavadia J, Ibrahim Q, Sookram S, Brass N, Knapp D, Welsh RC. Bridging the Gap for Nonmetropolitan STEMI Patients Through Implementation of a Pharmacoinvasive Reperfusion Strategy. Canadian Journal of Cardiology. 2013;29(8):951-9.
155. Silvain J, Vignalou JB, Beygui F, O'Connor SA, Barthelemy O, Boccara F, et al. Impact of transfer time on mortality in acute coronary syndrome with ST-segment elevation treated by angioplasty. Arch Cardiovasc Dis. 2012;105(12):639-48.
156. Siontis KC, Barsness GW, Lennon RJ, Holmen JL, Wright RS, Bell MR, et al. Pharmacoinvasive and Primary Percutaneous Coronary Intervention Strategies in ST-Elevation Myocardial Infarction (from the Mayo Clinic STEMI Network). Am J Cardiol. 2016;117(12):1904-10.
157. Smith LG, Duval S, Tannenbaum MA, Johnson Brown S, Poulose AK, Iannone LA, et al. Are the results of a regional ST-elevation myocardial infarction system reproducible? Am J Cardiol. 2012;109(11):1582-8.
158. Sung GY, Bosson N, Kaji A, Eckstein M, Shavelle D, French W, et al. Therapeutic Hypothermia After Resuscitation From a Non-Shockable Rhythm Improves Outcomes in a Regionalized System of Cardiac Arrest Care. Neurocritical Care. 2016;24(1):90-6.
159. Tarkin J, Malhotra A, Apps A, Smith R, Di Mario C, Rogers P, et al. Inter-hospital transfer for primary angioplasty: delays are often due to diagnostic uncertainty rather than systems failure and universal time metrics may not be appropriate. EuroIntervention. 2015;11(5):511-7.
160. Tatu-Chitoiu GP, Arafat R, Deleanu D, Vinereanu D, Udroiu C, Petris A. Impact of the Romanian national programme for interventional therapy in ST-elevation myocardial infarction. EuroIntervention. 2012;8(Supp P):126-32.
161. Thiele H, Eitel I, Meinberg C, Desch S, Leuschner A, Pfeiffer D, et al. Randomized comparison of pre-hospital-initiated facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention in acute myocardial infarction very early after symptom onset: the LIPSIA-STEMI trial (Leipzig immediate prehospital facilitated angioplasty in ST-segment myocardial infarction). JACC Cardiovasc Interv. 2011;4(6):605-14.
162. Tideman PA, Tirimacco R, Senior DP, Setchell JJ, Huynh LT, Tavella R, et al. Impact of a

regionalised clinical cardiac support network on mortality among rural patients with myocardial infarction. Med J Aust. 2014;200(3):157-60.
163. Ting HH, Rihal CS, Gersh BJ, Haro LH, Bjerke CM, Lennon RJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI Protocol. Circulation. 2007;116(7):729-36.
164. Ting R, Tejpal A, Finken L, Fisher M, Lefkowitz C, Parthasarathy H, et al. Repatriation to referral hospital after reperfusion of STEMI patients transferred for primary percutaneous coronary intervention: Insights of a Canadian regional STEMI care system. Am Heart J. 2016;177:145-52.
165. Todt T, Thylen I, Alfredsson J, Swahn E, Janzon M. Strategies TO reduce time delays in patients with AcuTe coronary heart disease treated with primary PCI—the STOP WATCH study: a multistage action research project. BMJ Open. 2013;3:e003493.
166. Tomassini F, Gagnor A, Montali N, Infantino V, Tizzani E, Tizzani P, et al. Primary percutaneous coronary intervention without on-site cardiac surgery backup in unselected patients with ST-segment-Elevation Myocardial Infarction: The RIvoli ST-segment Elevation Myocardial Infarction (RISTEMI) registry. Cardiovasc Revasc Med. 2013;14(1):9-13.
167. Trimmel H, Bayer T, Schreiber W, Voelckel WG, Fiedler L. Emergency management of patients with ST-segment elevation myocardial infarction in Eastern Austria: a descriptive quality control study. Scand J Trauma Resusc Emerg Med. 2018;26(1):38.
168. Atary JZ, van der Hoeven BL, Borleffs CJW, van der Wall EE, Bax JJ, van Erven L, et al. Structured care for patients after acute myocardial infarction: sudden cardiac death prevention—data from the Leiden MISSION! AMI study. EP Europace. 2010;12(3):378-84.
169. van der Hoeven BL, Liem SS, Dijkstra J, Bergheanu SC, Putter H, Antoni ML, et al. Stent malapposition after sirolimus-eluting and bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: acute and 9-month intravascular ultrasound results of the MISSION! intervention study. JACC Cardiovasc Interv. 2008;1(2):192-201.
170. Von der Heidt A, Ammenwerth E, Bauer K, Fetz B, Fluckinger T, Gassner A, et al. HerzMobil Tirol network: rationale for and design of a collaborative heart failure disease management program in Austria. Wien Klin Wochenschr. 2014;126(21-22):734-41.
171. NHS Wales. Cardiovascular Atlas of Variation. Cardiff: NHS Wales, 2019.
172. Wilson BH, Humphrey AD, Cedarholm JC, Downey WE, Haber RH, Kowalchuk GJ, et al. Achieving sustainable first door-to-balloon times of 90 minutes for regional transfer ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2013;6(10):1064-71.
173. Yayehd K, Ricard C, Ageron FX, Buscaglia L, Savary D, Audema B, et al. Role of primary care physicians in treating patients with ST-segment elevation myocardial infarction located in remote areas (from the REseau Nord-Alpin des Urgences [RENAU], Network). Eur Heart J Acute Cardiovasc Care. 2015;4(1):41-50.
174. Gilsenan S. Analysis of HIPE Cardiology data. Dublin: Department of Health, 2019.
175. Health Service Executive and Royal College of Physicians of Ireland. Acute Coronary Syndromes Programme - Model of Care. HSE and RCPI; 2012.
176. Health Service Executive and Royal College of Physicians of Ireland. Heart attack care in Ireland 2014 -Report of the national clinical programme for Acute Coronary Syndrome (ACS) on standardising treatment of patients with STEMI in 2014. HSE and RCPI; 2015.
177. Health Service Executive and Royal College of Physicians of Ireland. Heart Attack Care Ireland 2016. HSE and RCPI; 2018.
178. Dehmer GJ, Blankenship JC, Cilingiroglu M, Dwyer JG, Feldman DN, Gardner TJ, et al. SCAI/ACC/AHA Expert Consensus Document: 2014 update on percutaneous coronary intervention without on-site surgical backup. J Am Coll Cardiol. 2014;63(23):2624-41.
179. Jacobs AK, Normand SL, Massaro JM, Cutlip DE, Carrozza JP, Jr., Marks AD, et al. Nonemergency PCI at hospitals with or without on-site cardiac surgery. The New England journal of medicine. 2013;368(16):1498-508.
180. Aversano T, Lemmon CC, Liu L. Outcomes of PCI at hospitals with or without on-site cardiac surgery. The New England journal of medicine. 2012;366(19):1792-802.
181. Lee JM, Hwang D, Park J, Kim K-J, Ahn C, Koo B-K. Percutaneous coronary intervention at centers with and without on-site surgical backup: an updated meta-analysis of 23 studies. Circulation. 2015;132(5):388-401.
182. Central Statistics Office. Population 2011 to 2016 by Age Group, Sex, County and City and

Census Year https://www.cso.ie/px/pxeirestat/Statire/SelectVarVal/Define.asp?maintable=E3006&PLanguage=02019 [

183. Health Information and Quality Authority. Guidance on Developing Key Performance Indicators and Minimum Data Sets to Monitor Healthcare Quality: February 2013 (Version 1.1). Dublin: HIQA, 2013.
184. Fordyce CB, Ramanathan K, Park JE, Vandegriend RA, Cairns JA, Perry M, et al. Evolution of a regional stemi reperfusion model: The 6-year vancouver coastal health authority experience. Canadian Journal of Cardiology. 2014;30(10):S116.
185. Windecker S, Kolh P, Alfonso F, Collet J-P, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European heart journal. 2014;35(37):2541-619.
186. Statistical Institute of Catalonia. Indicadors geogràfics. Superfície, densitat i entitats de població http://www.idescat.cat/pub/?id=inddt&n=396&lang=en2019 [
187. Office for National Statistics. The countries of the UK https://webarchive.nationalarchives.gov.uk/20160108051201/http://www.ons.gov.uk/ons/guide-method/geography/beginner-s-guide/administrative/the-countries-of-the-uk/index.html2016 [
188. Spencer A, Ewing C, Cropper S. Making sense of strategic clinical networks. Archives of Disease in Childhood. 2013;98(11):843-5.
189. National Institute for Cardiovascular Outcomes Research. Myocardial Ischaemia National Audit Project. London: University College London, 2011.
190. National Institute for Cardiovascular Outcomes Research. Myocardial Ischaemia National Audit Project. London: University College London, 2014.
191. Ludman PF. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. Heart. 2011;97(16):1293-7.
192. British Cardiovascular Intervention Society. The National Audit of Percutaneous Coronary Interventions. London: BCIS, 2015.
193. Kristensen SD, Laut KG, Fajadet J, Kaifoszova Z, Kala P, Di Mario C, et al. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. Eur Heart J. 2014;35(29):1957-70.
194. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J. 2010;31(8):943-57.
195. Timmis A, Wilkins E, Wright L, Townsend N, Gale C, Grobbee R, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. European Heart Journal. 2017;39(7):508-79.
196. Christiansen T, Vrangbaek K. Hospital centralization and performance in Denmark-Ten years on. Health policy (Amsterdam, Netherlands). 2018;122(4):321-8.
197. Huitema AA, Harkness K, Heckman GA, McKelvie RS. The Spoke-Hub-and-Node Model of Integrated Heart Failure Care. Can J Cardiol. 2018;34(7):863-70.
198. McAlister FA, Lawson FM, Teo KK, Armstrong PW. A systematic review of randomized trials of disease management programs in heart failure. The American journal of medicine. 2001;110(5):378-84.
199. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. Journal of the American College of Cardiology. 2004;44(4):810-9.
200. Takeda A, Martin N, Taylor RS, Taylor SJ. Disease management interventions for heart failure. The Cochrane database of systematic reviews. 2019;1:Cd002752.
201. Allen JK, Dennison CR. Randomized trials of nursing interventions for secondary prevention in patients with coronary artery disease and heart failure: systematic review. Journal of Cardiovascular Nursing. 2010;25(3):207-20.
202. Rice H, Say R, Betihavas V. The effect of nurse-led education on hospitalisation, readmission,

quality of life and cost in adults with heart failure. A systematic review. Patient Educ Couns. 2018;101(3):363-74.

203. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. Archives of Internal Medicine. 2008;168(7):687-94.
204. Niznik JD, He H, Kane-Gill SL. Impact of clinical pharmacist services delivered via telemedicine in the outpatient or ambulatory care setting: A systematic review. Research in social & administrative pharmacy : RSAP. 2018;14(8):707-17.
205. Louis AA, Turner T, Gretton M, Baksh A, Cleland JG. A systematic review of telemonitoring for the management of heart failure. European journal of heart failure. 2003;5(5):583-90.
206. Clark RA, Inglis SC, McAlister FA, Cleland JG, Stewart S. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. Bmj. 2007;334(7600):942.
207. Chaudhry SI, Phillips CO, Stewart SS, Riegel B, Mattera JA, Jerant AF, et al. Telemonitoring for patients with chronic heart failure: a systematic review. Journal of cardiac failure. 2007;13(1):56-62.
208. Feltner C, Jones CD, Cené CW, Zheng Z-J, Sueta CA, Coker-Schwimmer EJ, et al. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. Annals of internal medicine. 2014;160(11):774-84.
209. Ertl G, Angermann CE, Bekeredjian R, Beyersdorf F, Güder G, Gummert J, et al. Structure and organization of heart failure networks (HF-NETs) and heart failure units (HFUs) to optimize treatment of acute and chronic heart failure: Joint recommendations of the DGK and the DGTHG for the treatment of heart failure. Kardiologe. 2016;10(4):222-35.
210. Luers C, Edelmann F, Wachter R, Pieske B, Mende M, Angermann C, et al. Prognostic impact of diastolic dysfunction in patients with heart failure with reduced ejection fraction: A cross-sectional analysis from the German Competence Network Heart Failure. Eur Heart J. 2014;35:1036.
211. Aspromonte N, Gulizia MM, Di Lenarda A, Mortara A, Battistoni I, De Maria R, et al. ANMCO/SIC Consensus Document: cardiology networks for outpatient heart failure care. European Heart Journal Supplements. 2017;19(suppl_D):D89-D101.
212. Wong GC, Welsford M, Ainsworth C, Abuzeid W, Fordyce CB, Greene J, et al. 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the Acute Management of ST-Elevation Myocardial Infarction: Focused Update on Regionalization and Reperfusion. Can J Cardiol. 2019;35(2):107-32.
213. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Canadian Medical Association Journal. 2010;182(18):E839-E42.
214. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. Canadian Medical Association Journal. 2010;182(10):E472-8.
215. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. Canadian Medical Association Journal. 2010;182(10):1045-52.
216. Feres F, Costa RA, Siqueira D, Ribamar Costa J, Chamié D, Staico R, et al. Guidelines of the Brazilian Society of Cardiology and the Brazilian Society of Hemodynamics and Interventional Cardiology on Percutaneous Coronary Intervention. Arquivos Brasileiros de Cardiologia. 2017;109(1):2541-619.
217. Avezum ÁJ, Feldman A, Carvalho ACdC, Sousa ACS, Mansur AdP, Bozza AEZ, et al. [V Guideline of the Brazilian Society of Cardiology on Acute Myocardial Infarction Treatment with ST Segment Elevation]. Arquivos Brasileiros De Cardiologia. 2015;105(2 Suppl 1):1-105.
218. Socialstyrelsen. [National Guidelines for Cardiac Care]: The Swedish National Board of Health and Welfare; 2018 [Available from: https://www.socialstyrelsen.se/SiteCollectionDocuments/2018-6-28-vetenskapligt-underlag.pdf.
219. Nikolaou NI, Arntz HR, Bellou A, Beygui F, Bossaert LL, Cariou A, et al. European Resuscitation Council Guidelines for Resuscitation 2015 Section 8. Initial management of acute coronary syndromes. Resuscitation. 2015;95:264-77.

220. Nikolaou NI, Welsford M, Beygui F, Bossaert L, Ghaemmaghami C, Nonogi H, et al. Part 5: Acute coronary syndromes. 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation. 2015;95:e121-e46.
221. Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, et al. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. Heart Lung and Circulation. 2016;25(9):895-951.
222. White H. ST-elevation myocardial infarction: New zealand management guidelines, 2013. New Zealand Medical Journal. 2013;126(1387):127-64.
223. The Cardiac Society of Australia and New Zealand (New Zealand Branch). New Zealand 2012 guidelines for the management of non ST-elevation acute coronary syndromes. New Zealand Medical Journal. 2012;125(1357):122-47.
224. Australian Rescucitation Council and New Zealand Rescucitation Council. ANZCOR Guideline 14.3 – Acute Coronary Syndromes: Reperfusion Strategy. ANZCOR, 2016.
225. Australian Commission on Safety Quality in Health Care. Acute Coronary Syndromes Clinical Care Standard. Sydney, NSW: ACSQHC; 2014.
226. Cardiovascular Health Nova Scotia. Nova Scotia Guidelines for Acute Coronary Syndromes. Halifax, NS: CVHNS; 2008.
227. Claeys MJ, Gevaert S, De Meester A, Evrard P, Legrand V, Vrints C, et al. Implementation of reperfusion therapy in ST Segment Elevation Myocardial Infarction (STEMI). a policy statement from the Belgian Society of Cardiology and its working group of acute cardiology and interventional cardiology. Revue Medicale de Bruxelles. 2010;31(1):30-4.
228. Clinical Practice Guidelines Secretariat. Clinical practice guidelines - Management of percutaneous coronary intervention (PCI). Putrajaya: Ministry of Health Malaysia, 2009.
229. Clinical Practice Guidelines Secretariat. Clinical practice guidelines - Management of acute ST segment elevation myocardial infarction (STEMI). Putrajaya: Ministry of Health Malaysia, 2014.
230. Dalal JJ, Alexander T, Banerjee PS, Dayasagar V, Iyengar SS, Kerkar PG, et al. 2013 consensus statement for early reperfusion and pharmaco-invasive approach in patients presenting with chest pain diagnosed as STEMI (ST elevation myocardial infarction) in an Indian setting. The Journal of the Association of Physicians of India. 2014;62(6):473-83.
231. de Oliveira MTJ, Canesin MF, Marcolino MS, Ribeiro ALP, de Carvalho ACC, Reddy S, et al. Telecardiology guideline for the care of patients with acute coronary syndrome and other heart diseases. Arquivos Brasileiros de Cardiologia. 2015;104(5):1-26.
232. Eisenhauer AC, Mort E. Guidelines for therapy of ST-segment-elevation acute myocardial infarction in patients presenting to partners healthCare system hospital emergency departments. Critical Pathways in Cardiology. 2008;7(1):11-20.
233. Guha S, Sethi R, Ray S, Bahl VK, Shanmugasundaram S, Kerkar P, et al. Cardiological Society of India: Position statement for the management of ST elevation myocardial infarction in India. Indian Heart Journal. 2017;69:S63-S97.
234. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2018;39(2):119-77.
235. Jneid H, Addison D, Bhatt DL, Fonarow GC, Gokak S, Grady KL, et al. 2017 AHA/ACC Clinical Performance and Quality Measures for Adults With ST-Elevation and Non–ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. 2017:23847.
236. Li YH, Yeh HI, Tsai CT, Liu PY, Lin TH, Wu TC, et al. 2012 Guidelines of the Taiwan Society of Cardiology (TSOC) for the management of ST-segment elevation myocardial infarction. Acta Cardiologica Sinica. 2012;28(1):63-89.
237. Nair T, Agrawal R, Bansal S, Dutta A, Ray R, Ray S. Expert consensus document on management of ST-Elevation myocardial infarction: Adaptation of 2012 ESC guidelines. Indian Journal of Critical Care Medicine. 2018;22(4):274-82.
238. National Institute for Health and Care Excellence. Acute coronary syndromes in adults [QS68]. NICE; 2014.
239. National Institute for Health and Care Excellence. Myocardial infarction with ST-segment

elevation: acute management. Clinical guideline CG167: NICE; 2013.
240. Cardiac Care Network. Quality-Based Procedures Clinical Handbook for Coronary Artery Disease. CCN of Ontario Ministry of Health and Long-Term Care, 2014.
241. O'Connor RE, Al Ali AS, Brady WJ, Ghaemmaghami CA, Menon V, Welsford M, et al. Part 9: Acute coronary syndromes: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132(18):S483-S500.
242. Promes SB, Glauser JM, Smith MD, Torbati SS, Brown MD. Clinical Policy: Emergency Department Management of Patients Needing Reperfusion Therapy for Acute ST-Segment Elevation Myocardial Infarction. Annals of emergency medicine. 2017;70(5):724-39.
243. Scottish Intercollegiate Guidelines Network. Acute coronary syndrome. Edinburgh: SIGN, 2016.
244. Tubaro M, Danchin N, Goldstein P, Filippatos G, Hasin Y, Heras M, et al. Pre-hospital treatment of STEMI patients. A scientific statement of the Working Group Acute Cardiac Care of the European Society of Cardiology. Acute Cardiac Care. 2011;13(2):56-67.
245. Rao SV, Tremmel JA, Gilchrist IC, Shah PB, Gulati R, Shroff AR, et al. Best practices for transradial angiography and intervention: A consensus statement from the society for cardiovascular angiography and intervention's transradial working group. Catheterization and Cardiovascular Interventions. 2014;83(2):228-36.
246. Goel PK, Menon A, Mullasari AS, Valaparambil AK, Pinto B, Pahlajani D, et al. Transradial access for coronary diagnostic and interventional procedures: Consensus statement and recommendations for India: Advancing Complex CoronariES Sciences through TransRADIAL intervention in India – ACCESS RADIAL™: Clinical consensus recommendations in collaboration with Cardiological Society of India (CSI). Indian Heart Journal. 2018;70(6):922-33.
247. Hamon M, Pristipino C, Di Mario C, Nolan J, Ludwig J, Tubaro M, et al. Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care** and Thrombosis of the European Society of Cardiology. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2013;8(11):1242-51.
248. Sianos G, Werner GS, Galassi AR, Papafaklis MI, Escaned J, Hildick-Smith D, et al. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2012;8(1):139-45.
249. Claeys MJ, Ahrens I, Sinnaeve P, Diletti R, Rossini R, Goldstein P, et al. Editor's Choice-The organization of chest pain units: Position statement of the Acute Cardiovascular Care Association. European Heart Journal: Acute Cardiovascular Care. 2017;6(3):203-11.
250. British Cardiovascular Intervention Society. Statement on the Development and Peer Review of New PCI Services. London, UK: BCIS, 2015.
251. The Cardiac Society of Australia and New Zealand. Position Statement: Competency in Percutaneous Coronary Intervention (PCI). CSANZ, 2014.
252. The Cardiac Society of Australia and New Zealand. Position Statement Performance of and Support Facilities for a Primary Percutaneous Coronary Intervention (PCI) Service. CSANZ, 2014.
253. The Cardiac Society of Australia and New Zealand. Guidelines on Support Facilities for Coronary Angiography and Percutaneous Coronary Intervention (PCI) including Guidelines on the Performance of Procedures in Rural Sites. CSANZ, 2016.
254. Banerjee AK, Kumar S. Guidelines for management of acute myocardial infarction. Journal of Association of Physicians of India. 2011;59(12 Special Issue):37-42.
255. Japanese Circulation Society (JCS). Guidelines for elective percutaneous coronary intervention in patients with stable coronary artery disease (JCS 2011) published in 2012: Digest version. Circulation Journal. 2013;77(6):1590-607.
256. Schächinger V, Nef H, Achenbach S, Butter C, Deisenhofer I, Eckardt L, et al. Guidelines to establish and operate catheterization laboratories and hybrid operating rooms/hybrid laboratories (3rd edition 2015): 3rd edition 2015. Kardiologe. 2015;9(1):89-123.
257. Berti S, Piccaluga E, Marchese A, Varbella F, Sardella G, Danzi GB, et al. SICI-GISE position

paper on standards and guidelines for diagnostic and catheterization laboratories. Giornale Italiano di Cardiologia. 2015;16(10):590-600.

258. Netherlands Society of Cardiology. Practice Document for interventional cardiology: NVVC; 2016 [Available from: https://www.nvvc.nl/Richtlijnen/2016_Praktijkdocument_interventiecardiologie-1.pdf.
259. Dudek D, Legutko J, Ochala A, Gil RJ, Araszkiewicz A, Lesiak M, et al. [Guidelines of the Association of Cardiovascular Interventions of the Polish Cardiac Society for certification of coronary diagnosts and percutaneous coronary intervention operators and invasive cardiology centers in Poland]. Kardiologia polska. 2013;71(12):1332-6.
260. Kaiser C, Cook S, Wenaweser P, Zellweger M, Pedrazzini G. Institutional and operator recommendations for percutaneous coronary interventions. Schweizerische Ärztezeitung. 2014;95(14).
261. NHS England. 2013/14 NHS Standard contract for cardiology: primary percutaneous coronary intervention (PPCI) (Adult): A09/S/d. NHS England; 2013.
262. Banning AP, Baumbach A, Blackman D, Curzen N, Devadathan S, Fraser D, et al. Percutaneous coronary intervention in the UK: recommendations for good practice 2015. Heart. 2015;101 Suppl 3:1-13.
263. MacCarthy P, Blackman D, Hildick-Smith D, Banning A. Primary Percutaneous Coronary Intervention for ST Elevation Myocardial Infarction Position statement for Facilities and Emergency Medical Staffing July 2016. British Cardiovascular Intervention Society, 2016.
264. Cardiac Care Network. Recommendations for the best-practice STEMI management in Ontario. CCN of Ontario Ministry of Health and Long-Term Care, 2013.
265. Canadian Cardiovascular Society. Quality Indicators for Percutaneous Coronary Intervention: A CCS Consensus Document. Ottawa, ON: CCS, 2015.
266. Bashore TM, Balter S, Barac A, Byrne JG, Cavendish JJ, Chambers CE, et al. 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions Expert Consensus Document on Cardiac Catheterization Laboratory Standards update: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Journal of the American College of Cardiology. 2012;59(24):2221-305.
267. Nallamothu BK, Tommaso CL, Anderson HV, Anderson JL, Cleveland JC, Jr., Dudley RA, et al. ACC/AHA/SCAI/AMA-Convened PCPI/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. J Am Coll Cardiol. 2014;63(7):722-45.
268. Naidu SS, Aronow HD, Box LC, Duffy PL, Kolansky DM, Kupfer JM, et al. SCAI expert consensus statement: 2016 best practices in the cardiac catheterization laboratory: (Endorsed by the cardiological society of india, and sociedad Latino Americana de Cardiologia intervencionista; Affirmation of value by the Canadian Association of interventional cardiology–Association canadienne de cardiologie d'intervention)*. Catheterization and Cardiovascular Interventions. 2016;88(3):407-23.
269. Rashid M, Mamas MA, Sperrin M, Ludman PF, O'Neill D, Nicholas O, et al. Impact of operator volume for percutaneous coronary intervention on clinical outcomes: what do the numbers say? European Heart Journal - Quality of Care and Clinical Outcomes. 2016;2(1):16-22.
270. Fanaroff AC, Zakroysky P, Wojdyla D, Sherwood MW, Roe MT, Wang TY, et al. Association between operator pci volume and long-term outcomes in older adults: A report from the NCDR CathPCI registry. Circulation. 2017;136.
271. Hulme W, Sperrin M, Curzen N, Kinnaird T, De Belder MA, Ludman P, et al. Operator volume is not associated with mortality following percutaneous coronary intervention: Insights from the British Cardiovascular Intervention Society registry. Eur Heart J. 2018;39(18):1623-34.
272. Andreassi MG, Piccaluga E, Guagliumi G, Del Greco M, Gaita F, Picano E. Occupational health risks in cardiac catheterization laboratory workers. Circulation: Cardiovascular Interventions. 2016;9(4):e003273.
273. Amato L, Fusco D, Acampora A, Bontempi K, Rosa AC, Colais P, et al. Volume and health outcomes: evidence from systematic reviews and from evaluation of Italian hospital data. Epidemiol Prev. 2017;41(5-6 (Suppl 2)):1-128.

274. Badheka AO, Panaich SS, Arora S, Patel N, Patel NJ, Savani C, et al. Percutaneous Coronary Intervention: Relationship Between Procedural Volume and Outcomes. Curr Cardiol Rep. 2016;18(4).
275. Kumbhani DJ, Bittl JA. Much Ado About Nothing?: The Relationship of Institutional Percutaneous Coronary Intervention Volume to Mortality. Am Heart Assoc; 2017.
276. Milstein A, Galvin RS, Delbanco SF, Salber P, Buck CR, Jr. Improving the safety of health care: the leapfrog initiative. Effective clinical practice : ECP. 2000;3(6):313-6.
277. Ko DT, Wijeysundera HC, Zhu X, Richards J, Tu JV. Canadian quality indicators for percutaneous coronary interventions. Can J Cardiol. 2008;24(12):899-903.
278. Kumbhani D, Bhatt DL. A New Dimension in the Relationship Between Procedural Volumes and Quality. Circulation. 2019;139(4):473-6.
279. Sanderson S, Tatt ID, Higgins J. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. International journal of epidemiology. 2007;36(3):666-76.
280. Health Informationand Quality Authority. Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland. Dublin, Ireland: HIQA, 2018.
281. Keeley EC, Hillis LD. Primary PCI for Myocardial Infarction with ST-Segment Elevation. New England Journal of Medicine. 2007;356(1):47-54.
282. Singh M, Lennon RJ, Gulati R, Holmes DR. Risk scores for 30-day mortality after percutaneous coronary intervention: new insights into causes and risk of death. Mayo Clinic proceedings. 2014;89(5):631-7.
283. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. 2008.
284. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). Journal of the American College of Cardiology. 2015;66(4):403-69.
285. Sterne JA, Bradburn MJ, Egger M. Meta–Analysis in Stata™. Systematic reviews in health care: meta-analysis in context. 2001:347-69.
286. GRADEpro. GRADEpro Guideline Development Tool [Software]: McMaster University (developed by Evidence Prime, Inc.); 2015 [Available from: https://gradepro.org/.
287. Schünemann H BJ, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, 2013 Available at: guidelinedevelopmentorg/handbook. 2013.
288. Adogwa O, Costich JF, Hill R, Slavova S. Does higher surgical volume predict better patient outcomes? J Ky Med Assoc. 2009;107(1):10-6.
289. Arora S, Panaich SS, Patel NJ, Patel N, Solanki S, Deshmukh A, et al. Multivessel Percutaneous Coronary Interventions in the United States. Angiology. 2016;67(4):326-35.
290. Badheka AO, Patel NJ, Grover P, Singh V, Patel N, Arora S, et al. Impact of annual operator and institutional volume on percutaneous coronary intervention outcomes: a 5-year United States experience (2005-2009). Circulation. 2014;130(16):1392-406.
291. Barnett PG, Hong JS, Carey E, Grunwald GK, Joynt Maddox K, Maddox TM. Comparison of Accessibility, Cost, and Quality of Elective Coronary Revascularization Between Veterans Affairs and Community Care Hospitals. JAMA Cardiol. 2018;3(2):133-41.
292. Fanaroff AC, Zakroysky P, Dai D, Wojdyla D, Sherwood MW, Roe MT, et al. Outcomes of PCI in Relation to Procedural Characteristics and Operator Volumes in the United States. Journal of the American College of Cardiology (JACC). 2017;69(24):2913-24.
293. Fanaroff AC, Zakroysky P, Wojdyla D, Kaltenbach LA, Sherwood MW, Roe MT, et al. Relationship Between Operator Volume and Long-Term Outcomes after Percutaneous Coronary Intervention: A Report from the NCDR CathPCI Registry. Circulation. 2018.
294. Kontos MC, Wang Y, Chaudhry SI, Vetrovec GW, Curtis J, Messenger J. Lower Hospital Volume Is Associated With Higher In-Hospital Mortality in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment–Elevation Myocardial Infarction: A Report From the NCDR. Circulation: Cardiovascular Quality and Outcomes. 2013:CIRCOUTCOMES. 113.000233.
295. Kumbhani DJ, Cannon CP, Fonarow GC, Liang L, Askari AT, Peacock WF, et al. Association of hospital primary angioplasty volume in ST-segment elevation myocardial infarction with

quality and outcomes. JAMA - Journal of the American Medical Association. 2009;302(20):2207-13.

296. Srinivas VS, Hailpern SM, Koss E, Monrad ES, Alderman MH. Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. Journal of the American College of Cardiology (JACC). 2009;53(7):574-9.
297. Qian F, Zhong Y, Hannan EL. Relationship between operator and hospital volumes and short-term mortality for percutaneous coronary intervention in New York. Int J Cardiol. 2019.
298. Kodaira M, Kuno T, Numasawa Y, Ohki T, Nakamura I, Ueda I, et al. Differences of in-hospital outcomes within patients undergoing percutaneous coronary intervention at institutions with high versus low procedural volume: A report from the Japanese multicentre percutaneous coronary intervention registry. Open Heart. 2018;5(2).
299. Inohara T, Kohsaka S, Yamaji K, Amano T, Fujii K, Oda H, et al. Impact of institutional and operator volume on short-term outcomes of percutaneous coronary intervention: A report from Japanese nationwide registry. J Am Coll Cardiol. 2017;69(11):1366.
300. Kuwabara H, Fushimi K, Matsuda S. Relationship Between Hospital Volume and Outcomes Following Primary Percutaneous Coronary Intervention in Patients With Acute Myocardial Infarction. Circulation Journal. 2011;75(5):1107-12.
301. Shiraishi J, Kohno Y, Sawada T, Arihara M, Hyogo M, Yagi T, et al. Effects of hospital volume of primary percutaneous coronary interventions on Angiographic results and in-hospital outcomes for acute myocardial infarction. Circulation Journal. 2008;72(7):1041-6.
302. Kubo S, Yamaji K, Inohara T, Kohsaka S, Tanaka H, Ishii H, et al. In-Hospital Outcomes After Percutaneous Coronary Intervention for Acute Coronary Syndrome With Cardiogenic Shock (from a Japanese Nationwide Registry [J-PCI Registry]). Am J Cardiol. 2019;123(10):1595-601.
303. O'Neill D, Nicholas O, Gale CP, Ludman P, de Belder MA, Timmis A, et al. Total Center Percutaneous Coronary Intervention Volume and 30-Day Mortality: A Contemporary National Cohort Study of 427 467 Elective, Urgent, and Emergency Cases. Circ Cardiovasc Qual Outcomes. 2017;10(3).
304. Kim YH, Her AY. Relationship between hospital volume and risk-adjusted mortality rate following percutaneous coronary intervention in Korea, 2003 to 2004. Anadolu Kardiyoloji Dergisi. 2013;13(3):237-42.
305. Navarese EP, De Servi S, Politi A, Martinoni A, Musumeci G, Boschetti E, et al. Impact of primary PCI volume on hospital mortality in STEMI patients: does time-to-presentation matter? J Thromb Thrombolysis. 2011;32(2):223-31.
306. Xu B, Redfors B, Yang Y, Qiao S, Wu Y, Chen J, et al. Impact of Operator Experience and Volume on Outcomes After Left Main Coronary Artery Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2016;9(20):2086-93.
307. Yu TH, Chou YY, Wei CJ, Tung YC. Are PCI service volumes associated with 30-day mortality? A population-based study from Taiwan. Int J Environ Res Public Health. 2017;14(11).
308. Zahn R, Gottwik M, Hochadel M, Senges J, Zeymer U, Vogt A, et al. Volume–outcome relation for contemporary percutaneous coronary interventions (PCI) in daily clinical practice: is it limited to high-risk patients? Results from the Registry of Percutaneous Coronary Interventions of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK). Heart. 2008;94(3):329-35.
309. Peterson ED, Dai D, DeLong ER, Brennan JM, Singh M, Rao SV, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol. 2010;55(18):1923-32.
310. Krumholz HM, Normand S-LT, Wang Y. Twenty-Year Trends in Outcomes for Older Adults With Acute Myocardial Infarction in the United StatesTwenty-Year Trends in Outcomes of Acute Myocardial Infarction in Older US AdultsTwenty-Year Trends in Outcomes of Acute Myocardial Infarction in Older US Adults. JAMA Network Open. 2019;2(3):e191938-e.
311. Myles PS. Meaningful outcome measures in cardiac surgery. The journal of extra-corporeal technology. 2014;46(1):23-7.
312. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, De Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;61(4):e78-e140.

313. Desai NR, Bradley SM, Parzynski CS, Nallamothu BK, Chan PS, Spertus JA, et al. Appropriate Use Criteria for Coronary Revascularization and Trends in Utilization, Patient Selection, and Appropriateness of Percutaneous Coronary InterventionTrends in Appropriateness of PCITrends in Appropriateness of PCI. JAMA. 2015;314(19):2045-53.
314. Critical Appraisals Skills Programme (CASP). CASP Appraisal Checklists 2018 [Available from: https://casp-uk.net/casp-tools-checklists/.
315. Fu R, Gartlehner G, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. Journal of clinical epidemiology. 2011;64(11):1187-97.
316. Dziewierz A, Brener SJ, Siudak Z, Plens K, Rakowski T, Zasada W, et al. Impact of On-Site Surgical Backup on Periprocedural Outcomes of Primary Percutaneous Interventions in Patients Presenting With ST-Segment Elevation Myocardial Infarction (From the ORPKI Polish National Registry). The American journal of cardiology. 2018;122(6):929-35.
317. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. New England Journal of Medicine. 2007;356(15):1503-16.
318. Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. The New England journal of medicine. 2013;369(10):901-9.
319. De Luca G, Suryapranata H, Zijlstra F, van't Hof AWJ, Hoorntje JCA, Gosselink ATM, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. Journal of the American College of Cardiology. 2003;42(6):991-7.
320. Mishra S. What is the ideal fibrinolysis to PCI time: Pharmaco-invasive strategy with streptokinase? Indian heart journal. 2017;69(5):569-70.
321. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet (London, England). 2006;367(9510):569-78.
322. Gershlick AH, Banning AP, Myat A, Verheugt FW, Gersh BJ. Reperfusion therapy for STEMI: is there still a role for thrombolysis in the era of primary percutaneous coronary intervention? The Lancet. 2013;382(9892):624-32.
323. Siddiqi TJ, Usman MS, Khan MS, Sreenivasan J, Kassas I, Riaz H, et al. Meta-Analysis Comparing Primary Percutaneous Coronary Intervention Versus Pharmacoinvasive Therapy in Transfer Patients with ST-Elevation Myocardial Infarction. The American journal of cardiology. 2018;122(4):542-7.
324. Liu F, Guo Q, Xie G, Zhang H, Wu Y, Yang L. Percutaneous Coronary Intervention after Fibrinolysis for ST-Segment Elevation Myocardial Infarction Patients: An Updated Systematic Review and Meta-Analysis. PloS one. 2015;10(11):e0141855.
325. Roule V, Ardouin P, Blanchart K, Lemaitre A, Wain-Hobson J, Legallois D, et al. Prehospital fibrinolysis versus primary percutaneous coronary intervention in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Critical Care. 2016;20(1):359.
326. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.
327. Kuss O. Statistical methods for meta-analyses including information from studies without any events—add nothing to nothing and succeed nevertheless. Statistics in Medicine. 2015;34(7):1097-116.
328. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane2019.
329. Pu J, Ding S, Ge H, Han Y, Guo J, Lin R, et al. Efficacy and Safety of a Pharmaco-Invasive Strategy With Half-Dose Alteplase Versus Primary Angioplasty in ST-Segment-Elevation Myocardial Infarction: EARLY-MYO Trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment-Elevation Myocardial Infarction). Circulation. 2017;136(16):1462-73.
330. Vyshlov EV, Sevastyanova DS, Krylov AL, Markov VA. Primary angioplastics and

pharmacoinvasive reperfusion in myocardial infarction: impact on clinical outcomes and the no-reflow phenomenon. Cardiovasc Ther Prev. 2015;14:17.

331. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. New England journal of medicine. 2013;368(15):1379-87.
332. Armstrong PW, Zheng Y, Westerhout CM, Rosell-Ortiz F, Sinnaeve P, Lambert Y, et al. Reduced dose tenecteplase and outcomes in elderly ST-segment elevation myocardial infarction patients: Insights from the STrategic Reperfusion Early After Myocardial infarction trial. Am Heart J. 2015;169(6):890-8.e1.
333. Gershlick AH, Westerhout CM, Armstrong PW, Huber K, Halvorsen S, Steg PG, et al. Impact of a pharmacoinvasive strategy when delays to primary PCI are prolonged. Heart. 2015;101(9):692-8.
334. Sinnaeve PR, Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Lambert Y, et al. ST-segment-elevation myocardial infarction patients randomized to a pharmaco-invasive strategy or primary percutaneous coronary intervention: Strategic Reperfusion Early After Myocardial Infarction (STREAM) 1-year mortality follow-up. Circulation. 2014;130(14):1139-45.
335. Bendary A, Tawfek W, Mahros M, Salem M. Primary PCI versus pharmaco-invasive strategy in patients with ST-Elevation myocardial infarction; A randomized clinical study. Journal of cardiovascular disease research. 2018;9(1):28-31.
336. Sanz Ruiz R. Comparison of Primary PCI vs. Post-thrombolysis PCI as Reperfusion Strategies in STEMI [Comparación de la angioplastia primaria frente a la angioplastia post-fibrinolisis en pacientes con infarto agudo de miocardio con elevación del segmento ST. El ensayo clínico GRACIA 4]. University of Valladolid; 2017.
337. Bessonov IS, Kuznetsov VA, Zyryanov IP, Musikhina NA, Sapozhnikov SS, Takkand AG, et al. [Percutaneous Coronary Intervention in Patients With Acute Myocardial Infarction With ST-Segment Elevation After Prehospital Thrombolysis]. Kardiologiia. 2016;56(2):5-10.
338. Victor SM, Subban V, Alexander T, G BC, Srinivas A, S S, et al. A prospective, observational, multicentre study comparing tenecteplase facilitated PCI versus primary PCI in Indian patients with STEMI (STEPP-AMI). Open Heart. 2014;1(1):e000133.
339. Victor SM, Vijayakumar S, Alexander T, Bahuleyan CG, Srinivas A, Selvamani S, et al. Two-year follow-up data from the STEPP-AMI study: A prospective, observational, multicenter study comparing tenecteplase-facilitated PCI versus primary PCI in Indian patients with STEMI. Indian Heart J. 2016;68(2):169-73.
340. Sierra-Fragoso AA, Galván-García JE, Vargas-Ramírez JF, Arboine-Aguirre LA, Muñoz-Consuegra CE, Zapata-Ruiz A, et al. Pharmacoinvasive strategy versus primary angioplasty in patients with acute ST-segment elevation myocardial infarction. Revista Mexicana de Cardiologia. 2018;29(3):126-33.
341. Shavadia J, Ibrahim Q, Sookram S, Brass N, Knapp D, Welsh RC. Bridging the gap for nonmetropolitan STEMI patients through implementation of a pharmacoinvasive reperfusion strategy. Can J Cardiol. 2013;29(8):951-9.
342. Kumbhani DJ, Alexander T, Nallamothu BK, Menon V, Ayers C, Mullasari AS, et al. Pharmacoinvasive Approach with Streptokinase in Low to Intermediate Risk ST-Elevation Myocardial Infarction Patients: Insights from the Tamil Nadu-STEMI Initiative. American journal of cardiovascular drugs. 2019:1-3.
343. Rashid M, Guron N, Bernick J, Chong AY, Dick A, Froeschl M, et al. Safety and efficacy of a pharmaco-invasive strategy in st-elevation myocardial infarction: A patient population study comparing a pharmaco-invasive strategy to a primary percutaneous coronary intervention strategy within a regional system. J Am Coll Cardiol. 2016;67(13):636.
344. Carrillo X, Fernandez-Nofrerias E, Rodriguez-Leor O, Oliveras T, Serra J, Mauri J, et al. Early ST elevation myocardial infarction in non-capable percutaneous coronary intervention centres: in situ fibrinolysis vs. percutaneous coronary intervention transfer. Eur Heart J. 2016;37(13):1034-40.
345. Andersson HB, Seth M, Gurm HS, Bates ER. Pre-hospital Transport Times and Outcomes After Different Reperfusion Strategies for ST-Elevation Myocardial Infarction. Am J Cardiol. 2019;123(3):375-81.
346. Caldeira D, Pereira H. Adjuvant antithrombotic therapy in ST-elevation myocardial infarction: A narrative review. Revista Portuguesa de Cardiologia (English Edition). 2019;38(4):289-97.

347. Sen S, Davies JE, Malik IS, Foale RA, Mikhail GW, Hadjiloizou N, et al. Why does primary angioplasty not work in registries? Quantifying the susceptibility of real-world comparative effectiveness data to allocation bias. Circulation: Cardiovascular Quality and Outcomes. 2012;5(6):759-66.
348. Guillermin A, Yan DJ, Perrier A, Marti C. Safety and efficacy of tenecteplase versus alteplase in acute coronary syndrome: a systematic review and meta-analysis of randomized trials. Arch Med Sci. 2016;12(6):1181-7.
349. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The Problem With Composite End Points in Cardiovascular Studies: The Story of Major Adverse Cardiac Events and Percutaneous Coronary Intervention. Journal of the American College of Cardiology. 2008;51(7):701-7.
350. Murugiah K, Nuti SV, Krumholz HM. STEMI care in LMIC: obstacles and opportunities. Global heart. 2014;9(4):429-30.
351. Danchin N, Coste P, Ferrieres J, Steg PG, Cottin Y, Blanchard D, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the french registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation. 2008;118(3):268-76.
352. Larson DM, Duval S, Sharkey SW, Garberich RF, Madison JD, Stokman PJ, et al. Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. Eur Heart J. 2012;33(10):1232-40.
353. Rogers WJ, Dean LS, Moore PB, Wool KJ, Burgard SL, Bradley EL, et al. Comparison of primary angioplasty versus thrombolytic therapy for acute myocardial infarction. The American Journal of Cardiology. 1994;74(2):111-8.
354. Sim DS, Jeong MH, Ahn Y, Kim YJ, Chae SC, Hong TJ, et al. Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention in Patients With ST-Segment-Elevation Myocardial Infarction: A Propensity Score-Matched Analysis. Circ Cardiovasc Interv. 2016;9(9).
355. Danchin N, Coste P, Ferrières J, Steg PG, Cottin Y, Blanchard D, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: Data from the French registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation. 2008;118(3):268-76.
356. Danchin N, Puymirat E, Steg PG, Goldstein P, Schiele F, Belle L, et al. Five-Year survival in patients with ST-Segment-elevation myocardial infarction according to modalities of reperfusion therapy: The French registry on acute ST-elevation and non-ST-Elevation myocardial infarction (FAST-MI) 2005 cohort. Circulation. 2014;129(16):1629-36.
357. Vora AN, Holmes DN, Rokos I, Roe MT, Granger CB, French WJ, et al. Fibrinolysis use among patients requiring interhospital transfer for ST-segment elevation myocardial infarction care: a report from the US National Cardiovascular Data Registry. JAMA Intern Med. 2015;175(2):207-15.
358. Viikila J, Lilleberg J, Tierala I, Syvanne M, Kupari M, Salomaa V, et al. Outcome up to one year following different reperfusion strategies in acute ST-segment elevation myocardial infarction: the Helsinki-Uusimaa Hospital District registry of ST-Elevation Acute Myocardial Infarction (HUS-STEMI). Eur Heart J Acute Cardiovasc Care. 2013;2(4):371-8.
359. Health Service Executive. Dublin Midlands Hospital Group Operational Plan 2018. Dublin: HSE, 2018.
360. Health Service Executive. Ireland East Hospital Group Operational Plan 2018. Dublin: HSE, 2018.
361. Health Service Executive. RCSI Hospitals Group Operational Plan 2018. Dublin: HSE, 2018.
362. Health Service Executive. Saolta University Health Care Group Operational Plan 2018. Galway: HSE, 2018.
363. Health Service Executive. South/South West Hospital Group Operational Plan 2018. Cork: HSE, 2018.
364. Health Service Executive. University of Limerick Hospital Group Operational Plan 2018. Limerick: HSE, 2018.
365. Herity N. Independent Clincial Review of Provision of a Second Catheterisation Laboratory at

University Hospital Waterford. Belfast: Belfast HSC Trust, 2016.
366. Droog E, Foley C, Healy O, Buckley C, Boyce M, McHugh S, et al. Perspectives on the underlying drivers of urgent and emergency care reconfiguration in Ireland. The International Journal of Health Planning and Management. 2018;33(2):364-79.
367. National Review of Specialist Cardiac Services. Survey of current cardiac services provided in acute public hospitals (Draft). Department of Health, 2019.
368. Jessup M, Albert NM, Lanfear DE, Lindenfeld J, Massie BM, Walsh MN, et al. ACCF/AHA/HFSA 2011 Survey Results: Current Staffing Profile of Heart Failure Programs, Including Programs That Perform Heart Transplant and Mechanical Circulatory Support Device Implantation. A Report of the ACCF Heart Failure and Transplant Committee, AHA Heart Failure and Transplantation Committee, and Heart Failure Society of America. 2011;57(20):2115-24.
369. Bakal JA, Kaul P, Welsh RC, Johnstone D, Armstrong PW. Determining the Cost Economic "Tipping Point" for the Addition of a Regional Percutaneous Coronary Intervention Facility. Canadian Journal of Cardiology. 2011;27(5):567-72.
370. Jollis JG, Al-Khalidi HR, Roettig ML, Berger PB, Corbett CC, Doerfler SM, et al. Impact of Regionalization of ST-Segment-Elevation Myocardial Infarction Care on Treatment Times and Outcomes for Emergency Medical Services-Transported Patients Presenting to Hospitals With Percutaneous Coronary Intervention: Mission: Lifeline Accelerator-2. Circulation. 2018;137(4):376-87.
371. Health Service Executive. Renal Unit Networks 2019 [Available from: https://www.hse.ie/eng/about/who/cspd/ncps/renal/renal-unit-networks/.
372. Health Service Executive. Pathway of care for Transcatheter Aortic Valve Implantation & Transcatheter Pulmonary Valve Replacement. Dublin: HSE, 2017.
373. Young C, Lambert L, Abel J, O'Neill BJ. Quality of Cardiac Care in Canada: Recommendations for Building a Sustainable Future. Can J Cardiol. 2018;34(6):800-3.
374. Faxon DP, Burgess A. Cardiovascular Registries. Circulation: Cardiovascular Interventions. 2016;9(4):e003866.

Appendices

Appendix 1 — Search terms for electronic databases

Table A.1: Search terms for RQ1

Details	Free Text Terms [Title/Abstract]	Thesauri Terms
1. Population: Adults (18 years or older) presenting with cardiac problems (including ACS, heart failure and heart arrhythmias), or with grown-up congenital heart disease in need of acute and chronic (including cardiac rehabilitation) cardiac services. Also included are adults requiring access to cardiac diagnostic, genetic testing and investigative services, as well as adults requiring access to cardiac syncope clinics, electrophysiology and catheterisation laboratories.	PCI OR percutaneous coronary intervention* OR coronary angiography OR coronary angiogram OR cardiac catheteri* OR STEMI OR NSTEMI OR ST-segment elevation myocardial infarction OR Non ST-segment elevation myocardial infarction OR angina OR Coronary Artery Interventional Procedures OR myocardial revasculari* OR Acute coronary syndrome* OR Revasculari* OR Myocardial Infarction OR Heart Attack OR interventional cardiolog* OR catheteri* laboratory OR Heart Failure OR cardiac failure OR Atrial Fibrillation OR Cardiac arrhythmia* OR heart arrhythmia* OR cardiac dysrhythmia* OR heart dysrhythmia* OR atrial flutter OR ECG OR electrocardiogram OR stress test OR cardiac syncope OR grown up congenital heart disease OR adult congenital heart disease OR cardiac rehab* OR Cardiac diagnos* OR ((cardiac genetic testing)) OR electrophysiology OR	MeSH: Percutaneous Coronary Intervention, Myocardial Infarction, Cardiac Catheterization, Heart Failure, Heart Defects Congenital, Arrhythmias Cardiac, Cardiac Rehabilitation, Cardiac Electrophysiology Emtree: Percutaneous Coronary Intervention/exp, Heart Infarction/exp, heart catheterization/exp, heart failure/exp, congenital heart disease/exp, heart arrhythmia/exp, heart rehabilitation/exp, CINAHL: myocardial revascularization/exp, angioplasty/exp, myocardial infarction/exp, heart catheterization/exp, heart failure/exp, Heart Defects Congenital/exp, Arrhythmia/exp, Rehabilitation Cardiac/exp, Electrophysiology Laboratories/exp
2. Intervention: clinical network of services	Hub-and-spoke OR spoke-hub-and-node OR Integrated Health Care System OR managed care OR health care management OR clinical network OR managed network OR integrated healthcare network* OR Integrated Service OR Regionalization OR Regionalisation OR Centralisation OR Centralization OR Reference Network* OR Reference Cent* OR Specialist Cardiac Service* OR Reconfiguration OR Regional variation or hospital merger OR hierarchy OR Economy of scale OR satellite hospital* OR Network of Networks OR Integrated care OR Vertical integration OR Sectoral Integration OR Intervention Network* OR Model of care OR Models of care OR Clinical pathway* OR Local Area Teams OR Heart Attack	MeSH: Delivery of Health Care Integrated, Health Care Reform, Health Facility Merger, centralized hospital services Emtree: regionalization/exp, centralization/exp, integrated health care system/exp, CINAHL: Health Care Delivery Integrated/exp, Health Care Reform/exp,

	Cent* OR Strategic Clinical Network* OR Chronic Care Model OR coordinated care OR STEMI Network* OR network OR shared care	
3. Setting: Hospital-led, and/or cardiologist-led	Secondary care OR hospital OR outpatient OR tertiary care OR cardiologist	MeSH: Hospitals, Secondary Care, Tertiary Healthcare, Cardiology Service Hospital, Outpatients, Cardiologist Emtree: hospital/exp, secondary health care/exp, tertiary health care/exp, outpatient/exp, cardiology service/exp, cardiologist/exp CINAHL: Hospitals/exp, Secondary Health Care/exp, Tertiary Health Care/exp, outpatients/exp, Cardiologists/exp
1 AND 2 AND 3 Limits/filters: - Date: since 2008 -For databases other than PubMed (exclude MEDLINE sources)		

Table A.2: Search terms for RQ2

Details	Free Text Terms [Title/Abstract]	Thesauri Terms
1. Population: Adult patients 18 years and older requiring PCI (primary or elective) for cardiac conditions	PCI OR percutaneous coronary intervention OR coronary angiography OR coronary angiogram OR cardiac catheteri* OR STEMI OR NSTEMI OR ST-segment elevation myocardial infarction OR Non ST-segment elevation myocardial infarction OR angina OR Coronary Artery Interventional Procedures OR myocardial revasculari* OR Acute coronary syndrome* OR Revasculari* OR Myocardial Infarction OR Heart Attack OR interventional cardiolog* OR catheteri* laboratory	*MeSH:* Percutaneous Coronary Intervention, Myocardial Infarction (mh:noexp), Cardiac Catheterization (mh:noexp) *Emtree:* Percutaneous Coronary Intervention/exp, Heart Infarction/mj, heart catheterization/mj *CINAHL:* MM myocardial revascularization, MH angioplasty+, MM myocardial infarction, MM heart catheterization
2. Guidelines, recommendations and standards	guideline*[Title] standard[Title] standards[Title] statement[Title] recommendation*[Title]	*MeSH*: Guideline [Publication Type], Practice Guideline [Publication Type] *Emtree:* Practice guideline/mj *CINAHL*: MM practice guidelines
1 AND 2 Limits/filters: - Date: since 2008		

Table A.3: Search terms for RQ3

Details	Free Text Terms [Title/Abstract]	Thesauri Terms
1. Population: Adults (18 years or older) requiring PCI (primary or elective) for cardiac conditions	Percutaneous Coronary Intervention*OR Percutaneous Coronary Revascularization* OR Coronary Balloon Angioplast*OR Transluminal Coronary Balloon Dilation OR Angioplast* OR Endoluminal Repair* OR Percutaneous Transluminal Angioplasty	*MeSH:* 'Percutaneous Coronary Intervention'[Mesh] OR Angioplasty[Mesh] *Emtree:* 'Percutaneous Coronary Intervention'/exp OR 'Angioplasty'/exp *CINAHL*: (MH 'Angioplasty' +)
2. Intervention: High volume hospital/ operator	'hospital volume*' OR 'admission volume*' OR 'procedural volume*' OR 'procedure volume*' OR 'Provider volume*' OR 'Institutional volume*' OR 'surgeon volume*' OR 'Operator volume*' OR 'Operative volume*' OR 'case volume*' OR 'operation rate*' OR 'surgical volume*' OR 'Workload*' OR Caseload* OR 'high volume*' OR 'higher volume*' OR 'low volume*' OR 'lower volume*' OR 'highest volume*' OR 'lowest volume*' OR regionalization* OR centralisation* OR centralization* OR regionalisation* OR 'health facility size' OR ((case AND load) OR (work AND load))	*MeSH:* High-Volume Hospitals[MeSH], Workload[MeSH] *Emtree:* High Volume Hospital/exp, High Volume Surgeon/exp, 'Workload'/exp *CINAHL*: (MH 'Workload')
3. Primary Outcomes: Mortality (all-cause within hospital or death within 30 days following PCI) Survival (minimum follow-up period of three months)	mortalit* OR morbidit* OR 'Survival Rate*' OR Survival OR complication* OR 'treatment outcome' OR 'Volume– outcome' OR (volume AND outcome) OR outcom* OR 'Outcome and Process Assessment'	*MeSH:* Mortality [Mesh] OR Morbidity [Mesh] OR Survival Rate [Mesh] OR Survival [Mesh] OR Disease-Free Survival [Mesh] OR Postoperative Complications [Mesh] OR Treatment Outcome [Mesh] OR Outcome and Process Assessment (Health Care)[Mesh] *Emtree:* 'Mortality '/exp OR 'Morbidity '/exp OR 'Survival Rate '/exp OR 'Survival '/exp OR 'Disease Free Survival '/exp OR 'Postoperative Complication '/exp OR 'Treatment Outcome '/exp *CINAHL*: (MH 'Mortality +') OR (MH 'Morbidity +') OR (MH 'Survival') OR (MH 'Postoperative Complications +') OR (MH 'Treatment Outcomes +') OR (MH 'Outcome assessment') OR (MH 'Process Assessment' (Health Care) +)
1 AND 2 AND 3 Limits/filters: - Date: since 2008		

Table A.4: Search terms for RQ4

Details	Free Text Terms [Title/Abstract]	Thesauri Terms
1. Population: Adults (18 years or older) diagnosed with STEMI	stemi OR "st-elevation myocardial infarction" OR "st-elevated myocardial infarction" OR "st-elevated MI" OR "st-elevation MI" OR "ST-segment elevation myocardial infarction" OR "ST-segment elevated myocardial infarction" OR "ST-segment elevation MI" OR "ST-segment elevated MI"	*MeSH (PubMed/Cochrane):* ST Elevation Myocardial Infarction[MeSH]) *Emtree (Embase*): 'ST segment elevation myocardial infarction'/exp *CINAHL Subject Headings (CINAHL):* n/a
2. Intervention: Pharmacoinvasive strategy	fibrinoly* OR thromboly* OR alteplase OR reteplase OR streptokinase OR tenecteplase OR lanoteplase OR urokinase OR anistreplase OR pharmacoinvasive OR pharmaco-invasive OR "early invasive" OR (early NEXT/1 (PCI OR "percutaneous coronary intervention*" OR angioplast*)) OR "early routine" OR (rescue NEXT/1 (PCI OR "percutaneous coronary intervention*" OR angioplast*)) OR "routine rapid transfer"	*MeSH (PubMed/Cochrane):* "Fibrinolysis"[Mesh] OR "Fibrinolytic Agents"[Mesh] OR "Thrombolytic Therapy"[Mesh]) *Emtree (Embase*): 'fibrinolytic agent'/exp, fibrinolysis/exp, 'blood clot lysis'/exp *CINAHL Subject Headings (CINAHL): (*MH "Fibrinolysis") OR (MH "Thrombolytic therapy")
3. Comparator: Primary PCI	(Primary NEXT/1 (PCI OR "percutaneous coronary intervention*" OR angioplast*)) OR PPCI	*MeSH (PubMed/Cochrane):* n/a *Emtree (Embase*): n/a *CINAHL Subject Headings (CINAHL): n/a*
4. Outcomes: Mortality (all-cause and cardiac), survival, Major adverse cardiac event / major adverse cardiac and cerebrovascular events (MACE/MACCE), Recurrent MI / re-infarction, Thrombolysis in myocardial infarction (TIMI) 3 flow, Cardiogenic shock, Stroke (haemorrhagic and ischaemic), Bleeding (major), heart failure, Healthcare utilisation , Health-related quality of life	mortalit* OR morbidit* OR "Survival Rate*" OR Survival OR complication* OR MACE OR MACCE OR "Major adverse cardiac event*" OR ("major adverse cardiac" NEXT/2 "cerebrovascular event*") OR (recurrent NEXT/1 (MI OR "myocardial infarction" OR "heart attack" or "AMI" or "STEMI")) OR "re-infarct*" OR reinfarct* OR TIMI OR "Thrombolysis in myocardial infarction" OR shock OR stroke OR bleed* OR haemorrhage OR hemorrhage OR (healthcare NEXT/1 utili*) (care NEXT/1 utili*) OR hospitali* OR (length NEXT/3 stay) OR LOS OR "bed night*") OR admission* OR "emergency department" OR "ED visit*)" OR outpatient OR "quality of life" or QoL OR HRQoL OR "GP visit*" OR "general practitioner" OR "Patient Reported Outcome Measure*" OR "patient reported outcome*" OR PROM OR "Heart failure" OR "CARDIAC FAILURE"	*MeSH (PubMed/Cochrane):* Mortality [Mesh] OR Morbidity [Mesh] OR Survival Rate [Mesh] OR Survival [Mesh] OR Disease-Free Survival [Mesh] OR Postoperative Complications [Mesh] OR "Shock, Cardiogenic"[Mesh] OR Stroke[Mesh] OR Hemorrhage[Mesh] OR "Patient Acceptance of Health Care"[Mesh] OR "Hospitalization"[Mesh] OR "Outpatients"[Mesh] OR "Quality of Life"[Mesh] OR "General Practitioners"[Mesh] OR "Patient Reported Outcome Measures"[Mesh] OR "Emergency Service, Hospital"[Mesh] OR "Heart Failure"[Mesh] *Emtree (Embase):* 'Mortality '/exp OR 'Morbidity '/exp OR 'Survival

		Rate '/exp OR 'Survival '/exp OR 'Disease Free Survival '/exp OR 'Postoperative Complication '/exp OR 'major adverse cardiac event'/exp OR 'heart reinfarction'/exp OR 'cardiogenic shock'/exp OR 'cerebrovascular accident'/EXP OR bleeding/exp 'health care utilization'/EXP or 'length of stay'/EXP, 'Hospital admission'/EXP, 'HOSPITALIZATION'/EXP OR 'emergency ward'/EXP, OR outpatient/EXP OR 'Quality of life'/EXP OR 'general practitioner'/EXP OR 'patient-reported outcome'/EXP OR 'heart failure/exp *CINAHL Subject Headings (CINAHL)*: (MH "Mortality +") OR (MH "Morbidity +") OR (MH "Survival") OR (MH "Postoperative Complications +") OR (MH "Shock, Cardiogenic") OR (MH "Stroke +") OR (MH "Hemorrhage+") OR (MH "Hospitalization+") or (MH "Length of Stay") OR (MH "Emergency Service+") OR (MH "Outpatient Service") OR (MH "Quality of Life+") OR (MH "Physicians, Family") OR (MH "Patient-Reported Outcomes") OR (MH "Heart Failure+")
5. Study design: RCTs and observational studies	RCT OR "clinical trial" OR "randomised controlled trial*" OR "randomized controlled trial*" OR "randomized control trial*" OR "randomised control trial*") OR randomi* OR placebo OR observational OR Cohort OR "Cross-Sectional" OR "Case-control" OR registry OR "Register*" or "real-world"	*MeSH (PubMed/Cochrane):* "Randomized Controlled Trials as Topic"[Mesh] OR "Observational Studies as Topic"[Mesh] OR "Cohort Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh] OR Case-Control Studies"[Mesh] OR "Registries"[Mesh] *Emtree (Embase):* randomized controlled trial/exp, OR observational study/exp OR cohort analysis/exp OR cross-sectional study/exp OR case control study/exp OR register/exp *CINAHL Subject Headings (CINAHL):* (MH "Randomized Controlled Trials+") OR (MH "Nonexperimental Studies+") OR

		(MH "Registries, Disease")
1 AND 2 AND 3 AND 4 AND 5 *Limits/filters:* *- Date: since 2008*		

Appendix 2 — Grey literature sources

Table A.5: Guideline internet sites, clearinghouses and other grey literature sources

Guideline Internet Sites	URL
Department of Health (including National Clinical Guidelines)	http://health.gov.ie
Health Service Executive (HSE)	www.hse.ie
Lenus	www.lenus.ie
Health Information and Quality Authority (HIQA)	www.hiqa.ie
National Institute for Health and Care Excellence (NICE)	http://www.nice.org.uk/page.aspx?o=ourguidance
Guidelines and Audit Implementation Network / The Regulation and Quality Improvement Authority	http://gain-ni.org/index.php/audits/guidelines
NHS Evidence (incorporating Scottish Intercollegiate Guidelines Network (SIGN) & Guidelines International Network (GIN))	www.evidence.nhs.uk
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/knowledge
Food and Drug Administration	http://www.fda.gov/cder/guidance/index.htm
Emergency Care Research Institute (ECRI) Guidelines Trust	https://guidelines.ecri.org/
New Zealand Guidelines Group	http://www.nzgg.org.nz
National Health and Medical Research Council (NHMRC) Australian Clinical Guidelines	www.clinicalguidelines.gov.au
Canadian Agency for Drugs and Technology in Health	http://www.cadth.ca
Canadian Medical Association Infobase	https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx
Haute Autorité de santé (HAS)	http://www.has-sante.fr/portail/jcms/c_6056/fr/recherche-avancee?portlet=c_39085&search_antidot=&lang=en&typesf=guidelines

Ontario Guidelines Advisory Committee (GAC) Recommended Clinical Practice Guidelines	http://www.gacguidelines.ca
Finnish Medical Society Duodecim	http://www.kaypahoito.fi
World Health Organisation	www.who.int/en
Australian National Health and Medical Research Council Clinical Practice	https://nhmrc.gov.au/about-us/publications
Canadian Medical Association InfoBase	https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx
Institute for Healthcare Improvement (IHI)	http://www.ihi.org/
Japan Council for Quality Health Care	https://jcqhc.or.jp/en/
Danish Health Authority – National Clinical Guidelines	https://www.sst.dk/en/national-clinical-guidelines/publications
Singapore Ministry of Health	https://www.moh.gov.sg/
Socialstyrelsen (Health and Medical Care and Social Services, Sweden)	https://www.socialstyrelsen.se/english
The Finnish Medical Society Duodecim	https://www.duodecim.fi/english/
Geneva Foundation for Medical Education and Research	https://www.gfmer.ch/000_Homepage_En.htm
Belgian Health Care Knowledge Centre	https://kce.fgov.be/
AETSA (Andalusian Agency for Health Technology Assessment)	http://www.aetsa.org/
German Institute of Medical Documentation and Information	https://www.dimdi.de/dynamic/en/dimdi/
HTAi vortal	https://www.htai.org/index.php?id=579
Google Scholar and Google	https://scholar.google.com/, https://www.google.ie
Health Research Board (HRB) Ireland;	http://www.hrb.ie/home/
National Coordinating Centre for Health Technology Assessment (NCCHTA)	https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/
Open Grey	http://www.opengrey.eu/
Canadian Ontario HTA	https://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment

Table A.6: Professional bodies' websites

Professional Body Internet Sites	URL
Ireland	
Irish Cardiac Society	https://www.irishcardiacsociety.com/pages/default.asp
Irish Heart Foundation	www.irishheart.ie
Royal College of Physicians Ireland	www.rcpi.ie
Irish Nurses Cardiovascular Association	http://www.incanursing.ie/
UK	
British Cardiovascular Society	https://www.bcs.com/pages/default.asp
British Cardiovascular Intervention Society	https://www.bcis.org.uk/
Society for Cardiothoracic Surgery in GB and Ireland	https://scts.org/
British Association for Nursing in Cardiovascular Care	https://www.bancc.org.uk/pages/default.asp
Europe	
European Association for Cardio-Thoracic Surgery	https://www.eacts.org/
European Society of Cardiology	www.escardio.org
North America	
American College of Cardiology	https://www.acc.org/guidelines
American Heart Association	https://www.heart.org/
American Association for Thoracic Surgery	https://aats.org
Society of Thoracic Surgeons	https://www.sts.org/
Canadian Cardiovascular Society	http://www.ccs.ca/en/
Canadian Association of Interventional Cardiology	http://caic-acci.org/
Canadian Council of Cardiovascular Nurses	https://www.cccn.ca/
Australia & New Zealand	
Cardiac Society of Australia and New Zealand	https://www.csanz.edu.au/
Australian & New Zealand Society of Cardiac & Thoracic Surgery	https://anzscts.org/
Australasian Cardiovascular Nursing College	http://www.acnc.net.au/
Other	
Society for Cardiovascular Angiography and Interventions (SCAI)	http://www.scai.org/Default.aspx

Appendix 3 — Table of characteristics and outcomes

Table A.7: Table of characteristics of included acute coronary syndrome-related syndrome, cardiac networks (RQ1)

Network Name	Studies	Year of establish-ment	Population served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
Australia												
Victoria†	(68)	NR	1.20	?	1/2	NR	26	?	1.20	NA	TTT	Improved TTT (pre-post)
Cairns, Queensland†	(146)	2015	0.28	?	1/NR	1	NR	X	0.280	0.280	Mo, TTT, C	Improvements in TTT (since implemented)
Townsville, Queensland†	(146)	2016	0.295	?	1/NR	1	NR	√	0.295	0.295	Mo, TTT, C	Improvements TTT (since implemented)
Mackay Base, Queensland†	(146)	2014	0.182	?	1/NR	0◇	NR	X	0.182	NA	Mo, TTT, C	Improvements TTT (since implemented)
Sunshine Coast University Hospital, Queensland†	(146)	2017	0.563	?	1/NR	1	NR	X	0.563	0.563	Mo, TTT, C	Improvements TTT (since implemented)
The Prince Charles Hospital, Queensland†	(146)	1995	0.90	?	1/NR	1	NR	√	0.90	0.90	Mo, TTT, C	Improvements TTT (since implemented)
Royal Brisbane and Womens Hospital, Queensland†	(146)	1997	0.90	?	1/NR	1	NR	X	0.90	0.90	Mo, TTT, C	Improvements TTT (since implemented)
Princess	(146)	1998	1.0	?	1/NR	1	NR	√	1.0	1.0	Mo, TTT,	Improvements

Network Name	Studies	Year of establish-ment	Populatio served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
Alexandra Hospital, Queensland†											C	TTT (since implemented)
Gold Coast University Hospital, Queensland†	(146)	2006	0.70	?	1/NR	1	NR	√	0.70	0.70	Mo, TTT, C	Improvements TTT (since implemented)
South Australia (Integrated Cardiovascular Clinical Network)†	(162)	2001-2008	0.60	?	7/66	NR	NR	?	0.085	NA	Mo	Improved Mo (pre-post)
Melbourne (Eastern Health Network)‡	(137)	2002	0.88	?	1/?	1	NR	?	0.880	0.880	R, TTT, Mo, C	No change in TTT (pre-post)
Austria												
Vienna	(45, 108, 113, 116, 120, 121)	2003	2.0	?	6/0	2◇	23	?	0.333	1.0	Mo, TTT, R, Me	Improved Mo and R (pre-post)
Eastern Austria STEMI network‡	(167)	2007	0.766	?	3/4	1◇	90	?	0.255	0.766	TTT, R, Mo	NR
Belgium												
National Belgian network‡	(90)	2007	10.0	√	25/47	25	47	?	0.40	0.40	TTT, R, Mo	Improved R and TTT. No change in Mo (pre-post)
Canada												

Network Name	Studies	Year of establish-ment	Population served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
Toronto (St Michaels Hospital STEMI network)‡	(164)	2008	NR	?	1/2	NR	NR	?	NA	NA	Mo, TTT, Me	NR
Hamilton Niagara Haldimand Brant (Local Health Integration Network)‡	(132)	2010	1.40	?	1/15	NR	NR	?	1.40	NA	R, Mo, C, TTT, Me	NR
British Columbia (Fraser Health Region)‡	(89)	2009	1.60	?	1/12	1	133	?	1.60	1.60	Mo, TTT	NR
Vancouver Coastal Health Authority‡	(99)	2007	NR	?	2/11	NR	NR	?	NA	NA	R, Mo, C, TTT	Improved R and TTT. No change in Mo. Deterioration in C (since implemented))
Alberta Vital Heart Response‡	(113, 154)	2005	1.80	?	2/26	2	NR	?	0.90	0.90	R, TTT, Mo, C	Unclear impact on TTT (since implemented))
Ottawa‡	(45, 126)	2005	0.80	?	1/4	1	11	?	0.80	0.80	Mo, C, TTT, R, H	NR

Network Name	Studies	Year of establish-ment	Populatio served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
Croatia												
National Croatian primary PCI network‡	(76, 110, 140)	2005	4.284	?	11/NR	NR	NR	√	0.389	NA	Mo, C, TTT	Unclear impact on TTT. No change on Mo. Deterioration in C (since implemented)
Czech Republic												
National Czech Network†	(121)	NR	10.467	?	22/NR	22	NR	?	0.476	0.476	NR	NR
Liberac Post-Cardiac Arrest Care network†*	(153)	2016	0.441	?	1/7	1	NR	?	0.441	0.441	N, Mo	No change in Mo and N (pre-post)
Denmark												
Eastern Denmark STEMI network†±	(91, 121, 152)	2011	2.50	?	1/?	1	NR	√	2.50	2.50	TTT, Mo, R	Improved R and TTT. No change in Mo (pre-post)
France												
French Northern Alps (RESURCOR)‡	(88, 122, 173)	2002	1.86	?	3≠/?	3	132	?	0.620	0.620	R, TTT, Mo, H, C, Me	Improved R. Unclear impact on Mo (pre-post)
Greater Paris Area‡	(113, 125, 155)	NR	12.0	√	8/NR	8	NR	√	1.50	1.50	TTT, R, Mo	NR
Germany												
Essen (HIVE)‡	(84, 87, 106, 107,	2004	0.60	?	5/?	5	NR	√	0.120	0.120	Mo, TTT, R, H, C, Me	NR

Network Name	Studies	Year of establish-ment	Populatio served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
	115)											
Cologne (Kolner Infarkt Model)‡	(131, 145)	2005	1.0	?	5/11	5	NR	?	0.20	0.20	Mo, TTT, C, Me	Improved TTT and Mo (pre-post)
Leipzig (LIPSIA-STEMI network)‡	(45, 161)	2006	NR	?	3/19	NR	70	?	NA	NA	Mo, C, Me, TTT	NR
Gottingen‡	(151)	2005	0.30	?	1/2	1	26	?	0.30	0.30	TTT	Improved TTT (since implemented)
Rostock‡	(79, 80)	2002	0.35	?	1/5	1	27	?	0.350	0.350	TTT, R, Mo, C	Improved R,TTT and Mo (pre-post)
Ireland												
National ACS programme†	(174-177)	2013	4.6	?	9/28	5◇	NR	√	0.511	0.920	TTT, R, Mo, H, Me	Improved R, TTT and Mo. No change in H (since implemented)
Italy												
Emilia - Romagna†	(38-40, 42, 43)	2003-2004	4.10	√	10/38	10	63	?	0.410	0.410	TTT, Mo, C, H, Me	Improved Mo. No change in TTT (since implemented)
Bologna†	(41, 45-47, 144)	2003-2004	1.0	√	2/10	2	63	?	0.50	0.50	TTT, C, R, Mo, Me	Improved R, Mo and C (pre-post)
Veneto†	(149, 150)	2008	5.385	√	7/20+	7	NR	√	0.769	0.769	Mo, H, R, TTT	Improved TTT. Unclear impact on Mo (pre-

Network Name	Studies	Year of establish-ment	Populatio served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
												post)
Apulia†¥	(85, 86, 149, 150)	2004	4.0	√	15/?	15	NR	?	0.267	0.267	NR	NR
Arezzo‡	(97)	2003	0.350	√	1/4	1	35	?	0.350	0.350	R, TTT, Mo, C	Improved R, Mo and C. No change in TTT. (pre-post)
Milan‡	(105)	2001	3.90	√	19/4	19	NR	?	0.205	0.205	Mo, TTT	NR
Ristemi‡	(166)	NR	0.583	?	1/5	1	NR	X	0.583	0.583	Mo, C	NR
Japan												
Kumamoto†±	(139)	2012	NR	?	2/12	NR	156	√	NA	NA	NR	NR
New Zealand												
Auckland/ Northland‡	(128)	2006	1.610	?	3/7	1◇	430	√	0.537	1.610	TTT, Mo, Me	NR
Poland												
Malopolska‡	(94, 95)	2005	3.20	?	3/25	3	NR	?	1.067	1.067	TTT, Mo, C, R	Improved Mo, R. Unclear impact on TTT (pre-post)
Portugal												
Algarve (Green Lane for AMI)‡	(45, 104)	2004	0.50	?	1/5	1	80	?	0.50	0.50	Mo, C, TTT, R, Me	NR
Romania												
Tîrgu Mureș‡	(77, 78,	2004	1.130	?	1/13	1	212	?	1.130	1.130	TTT, Mo,	Improved R, D

Network Name	Studies	Year of establish-ment	Population served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
	142)										Me	and Mo (since implemented)
National Romanian STEMI network‡	(160)	2010	19.0	?	10/NR	10	NR	?	1.90	1.90	Mo, R, Me	NR
Spain												
Catalonia (Codi Infart STEMI network)‡	(48-51, 53, 54)	2009	7.50	?	10/?	5◇	NR	?	0.750	1.50	Mo, TTT, R, C, Me, H	Improved R, H, Mo. No change in C (pre-post)
Galicia (PROGALIAM network)‡	(54, 114)	2006	2.750	?	3/11	NR	NR	?	0.917	NA	Mo, TTT	NR
Sweden												
National Swedish STEMI network‡	(121)	NR	9.234	?	29/NR	12◇	NR	?	0.318	0.770	R, Mo, TTT	Improved R (pre-post)
Östergötland county (STOP-WATCH)‡	(165)	2005	0.430	√	1/2	1	45	?	0.430	0.430	TTT, R	Unclear impact on TTT (since implemented)
The Netherlands												
Midden (MISSION! Network)† ¥	(45, 71, 74, 75, 81, 109, 127, 168, 169)	2004	0.750	?	1/6	1	NR	?	0.750	0.750	TTT, Mo, H, Me, C	Improved TTT (pre-post)
National Dutch Network‡	(121)	NR	16.491	?	25/NR	25	NR	√	0.660	0.660	NR	NR

Network Name	Studies	Year of establish-ment	Populatio served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
UK												
Greater Glasgow and Clyde†±	(98)	NR	1.200	?	1/7	NR	NR	√	1.20	NA	Mo, R, H	NR
University Hospital of Wales†	(96, 171)	2012	NR	?	1/NR	1	NR	?	NA	NA	TTT, Mo, R, C	NR
London (ARREST network)‡†*	(143)	2018	NR	?	7/26	7	NR	?	NA	NA	Mo, N	NR
London (Heart Attack Centres)‡	(147, 159)	NR	NR	?	8/NR	8	NR	?	NA	NA	Mo, C, TTT	NR
London (Harefield Hospital)‡	(92)	2004	1.0	√	1/3	1	15	√	1.0	1.0	TTT, Mo, R	Improved Mo and R. Unclear impact on TTT (pre-post)
Northern Ireland‡	(112)	2011	NR	?	2/NR	2	NR	?	NA	NA	TTT, Mo	NR
US												
Los Angeles‡ *	(82, 100, 148, 158)	2006 (2010 for OHCA network)	10.0	?	33/?	33	NR	√	0.303	0.303	TTT, Mo, N	Improved TTT (pre-post)
Minneapolis (Heart Institute network)‡*	(45, 100, 111, 113, 130, 136,	2003 (2006 for OHCA networ	0.90	?	1/30	1	338	?	0.90	0.90	TTT, Mo, R, N	NR

Network Name	Studies	Year of establish-ment	Populatio served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
	157)	k)										
Minnesota (St. Cloud STEMI Network)‡	(72)	2004	NR	?	1/25	NR	160	?	NA	NA	TTT, Mo, R, C, Me	NR
North Carolina (RACE program)‡	(45, 100, 102, 103, 113, 117, 118, 138)	2006-2008	9.40	?	21/98	21	NR	√	0.448	0.448	TTT, Mo, R	Improved TTT and R. No change in Mo or C (pre-post)
Iowa Heart Centre STEMI network‡	(157)	2004	NR	?	1/23	1	193	?	NA	NA	TTT, Mo, R	NR
Dallas County STEMI network‡	(93, 100, 123, 124)	2010	5.50	?	15/?	14◇	NR	?	0.367	0.393	TTT, Mo, R, H, Me	Improved TTT (pre-post)
Washington D.C. (CodeHeart STEMI network)‡	(133)	2006	NR	?	1/15	1	NR	?	NA	NA	TTT, Mo, C	Improvements TTT (since implemented)
Illinois (Stat Heart Program)‡	(70)	2005	NR	?	2/6	2	141	?	NA	NA	TTT, Mo, R, C, H	NR
Mayo Clinic network‡	(45, 113, 156, 163)	2004	NR	?	1/43	1	241	?	NA	NA	Mo, TTT, R, C	NR
Charlotte, North Carolina	(172)	2008-2011	5.0	√	1/9	1	80	?	5.0	5.0	TTT, H, Mo	Improved TTT. No change in

Network Name	Studies	Year of establish-ment	Population served (millions)	Hub and spoke model	Number of PCI centres/ Number of non-PCI centres	Number of 24/7 centres	Maximum distance from PCI centre to non-PCI centre (km)	Surgical back up	Population per PCI centre (millions)	Population per 24/7 PCI centre (millions)	Key Performance Indicators	Author reported temporal changes
(Carolinas Healthcare System)‡												H and Mo (pre-post)
Orange County, California‡	(148)	2005	3.0	?	12/13	NR	NR	?	0.250	NA	TTT	NR
Marin County California‡	(148)	2003	0.30	?	1/2	NR	NR	?	0.30	NA	TTT	NR
San Diego County California‡	(148)	2007	3.0	?	13/7	NR	NR	?	0.231	NA	TTT	NR
Charlotte, North Carolina (Mecklenburg & Union County)‡	(148)	2007	1.0	?	3/4	NR	NR	?	0.333	NA	TTT	NR
Medford, Oregon (Jackson & Josephine County)‡	(148)	2006	0.30	?	1/3	NR	NR	?	0.30	NA	TTT	NR
Ventura County California‡	(148)	2007	0.80	?	3/4	NR	NR	?	0.267	NA	TTT	NR
Atlanta, Georgia (Fulton County)‡	(148)	2007	0.80	?	5/8	NR	NR	?	0.160	NA	TTT	NR
St. Paul's Minnesota‡	(148)	2006	0.80	?	3/12	NR	NR	?	0.267	NA	TTT	NR

Key: ACS – Acute coronary syndrome; AMI – Acute myocardial infarction; ARREST - A Randomized tRial of Expedited transfer to a cardiac arrest center for non-ST elevation OHCA; HIVE - Herzinfarktverbund Essen; LIPSIA-STEMI - Leipzig immediate prehospital facilitated angioplasty in ST-segment myocardial infarction; PROGALIAM - El programa gallego de atención del infarto agudo de miocardio con elevación del segmento ST; NA – not applicable; NR – not reported; NSTEMI – non ST elevation myocardial infarction; OHCA – Out of Hospital Cardiac Arrest; PCI – percutaneous coronary intervention; RACE - Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Department; RESURCOR - RESeau d'URgences CORonariennes; STEMI – ST elevation myocardial infarction; STOP-WATCH - Strategies TO reduce time delays in patients with AcuTe coronary heart disease treated with primary PCI; ? – Unclear; √ - Yes; X – No.

* Linked with an OHCA network.

± Linked with a Cardiac Surgery network.

¥ Linked with a Cardiac Arrhythmia network.

≠Fifteen acute hospitals and 12 hospitals dispatching mobile intensive care units (MICU) are also contained in this network.

+There are also 40 'node in the net' facilities in this network.

†Denotes ACS network that includes protocols for STEMI patients as well as for NSTEMI and/or unstable angina patients.

‡Denotes STEMI network that specifically focuses on protocols for STEMI patients only.

‡†Denotes NSTEMI network that specifically focuses on protocols for NSTEMI patients only.

◊Denotes the presence of part-time PCI centres within network.

C – PCI Complications; H – Healthcare utilisation; Me – Medications; Mo – Mortality/survival; N – Neurological function; R – Reperfusion strategy; TTT – time-to-treatment.

Table A.8: Table of characteristics of other (non-ACS) included cardiac networks (RQ1)

Network name	Studies	Cardiac condition	Year of establish-ment of network	Population served (millions)	Hub an spoke Model	Structure of network	Intervention components	Number 24/7 centres	Surgical back- up	Key Performance Indicators	Author reported temporal changes
Austria											
Innsbruck (HerzMobil Tirol Network)	(134, 135, 170)	HF	2012	NR	NA	1 tertiary referral centre, 3 primary referral centres and 2 dedicated HF outpatient clinics	Patient education. Telemedicine - mHealth monitoring. Assigned to a network physician in community. Link with in-hospital physicians. Nurse-led home visit	NA	NA	H, Mo	NR
Canada											
Ontario (SPARC)	(83)	OHCA	2007	6.60	?	2 academic health sciences centres and 27 other hospitals	Postcardiac Arrest Consult Team intervention: • targeted temperature management, • assessment for PCI electrophysiology assessment • appropriately delayed neuro-prognostication	2	?	R, Mo, N	No change in Mo, R or N (pre-post)
France											
East Paris (RESICARD)	(73)	HF	2002	NR	NA	4 hospitals an and unknown number of	MDT management. Enhanced medical care between GPs and cardiologists. Outpatient	NR	NA	Mo, H	No change in Mo or H (pre-post)

Network name	Studies	Cardiac condition	Year of establish-ment of network	Population served (millions)	Hub an spoke Model	Structure of network	Intervention components	Number c 24/7 centres	Surgical back- up	Key Performance Indicators	Author reported temporal changes
						GP centres and outpatient clinics	medical co-ordinator				
Spain											
Barcelona (Hospital Moises Brogg)	(101)	Chronic IHD and AF	2014	0.421	?	1 regional hospital and 19 primary care centres	Co-ordinated care between cardiologists and GPs. Telemedicine consultation.	NA	NA	Me, H, TTT	Improved TTT, H and Me (pre-post)
Sweden											
Swedish ACHD network	(141)	ACHD	NR	NR	NA	2 national referral centres and an unknown number of referral sites	Service provision	NR	√	Mo, C, H	NR
UK											
North West of England, North Wales and Isle of Man ACHD network	(129)	ACHD	2018	NR	NA	8 hospitals (4 hospital deliver Level 1 Specialist ACHD surgical service, 2 hospital deliver	Service provision	4	√	NR	NR

Network name	Studies	Cardiac condition	Year of establish-ment of network	Population served (millions)	Hub an spoke Model	Structure of network	Intervention components	Number 24/7 centres	Surgical back- up	Key Performance Indicators	Author reported temporal changes
						Level 2 Specialist ACHD cardiology service, 2 hospitals deliver level 3 ACHD outpatient services)					
US											
Pennsylvania (TREAT)*	(69)	OHCA	2013	NR	√	1 hub hospital and 2 spoke hospitals	Telemedicine consultation	1	NA	TTT, Me	NR

Key: ACHD – Adult congenital heart disease; AF – Atrial fibrillation; AMI – Acute myocardial infarction; ARREST - A Randomized tRial of Expedited transfer to a cardiac arrest center for non-ST elevation OHCA; HF – Heart failure; IHD – Ischaemic heart disease; MDT – Multidisciplinary team; NA – not applicable; NR – not reported; OHCA – Out of Hospital Cardiac Arrest; PCI – Percutaneous coronary intervention; RESICARD - Réseau Paris-Est pour la prise en charge des patients en insuffisance cardiaque; SPARC - Strategies for Post-Arrest Care; STEMI – ST elevation myocardial infarction; TREAT - Telemedicine Resuscitation and Arrest Trial; ? – Unclear; √ - Yes; X – No.
* Linked with a severe sepsis network.
C – PCI/procedural complications; H – Healthcare utilisation; Me – Medications; Mo – Mortality/survival; N – Neurological function; R – Reperfusion strategy; TTT – time-to-treatment.

Table A.9: Table of characteristics for RQ2

Organisation (year)	Type of document	Development team composition	Funding	Methods to evaluate evidence	Search dates	Methods for formulating recommendations
Asia-Pacific						
CSANZ (2014a)	Position statement	NR	NR	NR	NR	NR
CSANZ (2014b)	Position statement	NR	NR	NR	NR	NR
CSANZ (2016)	Guideline	NR	NR	Based on international guidelines	NR	NR
API (2011)	Guideline	2 members: a senior consultant/intervention cardiologist and a Professor of Cardiology	NR	Based on international guidelines	NR	NR
JCS (2013)	Guideline	**JCS Joint Working Group** 20 members **Coronary Revascularisation Council** 14 members: interventional cardiologists, cardiac surgeons and diabetes specialists	NR	NR	NR	■ Expert consensus (by the Coronary Revascularization Council) ■ The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to predefined scales*
Europe						
ESC/EACTS (2019)	Guideline	22 members: professionals involved with the medical care of patients with this pathology	The ESC and EACTS	■ Selected experts in the field undertook a comprehensive review of the published evidence. ■ A critical evaluation of diagnostic and therapeutic procedures was performed including assessment	NR	The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to predefined scales*

Organisation (year)	Type of document	Development team composition	Funding	Methods to evaluate evidence	Search dates	Methods for formulating recommendations
				of the risk–benefit ratio. ■ Estimates of expected health outcomes for larger populations were included, where data exist.		
DGK (2015)	Guideline	18 members	NR	NR	NR	NR
HSE/RCPI (2012)**	Programme model of care (guideline)	11 members: doctors, public health specialists, nurses, emergency services professionals and researchers	NR	NR	NR	NR
SICI-GISE (2015)	Position paper	12 members	NR	NR	NR	NR
NVVC (2016)	Practice Document	NR	NR	Based on previous EAPCI and ESC documents	NR	Expert consensus
PTK (2013)	Guideline	14 members: cardiologists, academics, haematologists	NR	NR	NR	Expert consensus
SSC (2014)	Position paper	5 members	NR	Based on international guidelines, national recommendations and on expert consensus	NR	NR
NHS England (2013)	Service specification document	NR	NR	NR	NR	Expert consensus
BCIS and BCS (2015)	Guideline/ Consensus statement	11 members	NR	NR	NR	NR
BCIS (2016)	Position statement	4 members: consultant cardiologists (n=2); interventional cardiologist (n=1); consultant (n=1)	NR	NR	NR	NR
North America						
CCN (2013)	Consensus document	21 members: general cardiologists, interventional	NR	■ Documenting best practices based on existing literature and,	NR	Expert consensus

Organisation (year)	Type of document	Development team composition	Funding	Methods to evaluate evidence	Search dates	Methods for formulating recommendations
		cardiologists, hospital administrators and representatives of emergency medical services		where no published literature was available, on the expert consensus opinion of the Working Group members. ■ 3 web-based surveys		
CCS (2015)	Consensus document	11 members	Public Health Agency of Canada	NR	NR	Informal expert consensus via web consultation
ACCF/SCAI (2012)	Consensus document	16 members: ACCF (n=12); SCAI (n=3); STS (n=1); SVM (n=1); radiation physicist expert (n=1). Acknowledged experts in cardiovascular catheterisations and interventions; from both the academic and private practice sectors; representing a diverse geography.	ACCF		NR	Expert consensus via conference call and email
ACCF/AHA/SCAI (2013)	Clinical competence statement	19 members: identified through a comprehensive list of attributes	ACCF	Systematic review and expert opinion	Since January 1990 - no end date reported	Expert consensus via conference call and email
SCAI/ACC/AHA (2014)	Consensus document	8 members	NR	Systematic review and previous guidelines/expert consensus documents	2006-2014	Expert consensus
ACC/AHA/SCAI/	Performance measures	23 members: clinicians specializing in	The ACC, the AHA,	Expert consensus based on information from previous	NR	■ Expert consensus ■ Feedback from peer

Organisation (year)	Type of document	Development team composition	Funding	Methods to evaluate evidence	Search dates	Methods for formulating recommendations
AMA (2014)	report	interventional cardiology, general cardiology, internal medicine, cardiac surgery, and cardiac rehabilitation, as well as individuals with expertise in guideline development and performance measure development, implementation, and testing. Also included patient/consumer and payer representatives.	and the AMA	guidelines/expert consensus documents		review and public comment period
SCAI (2016)	Consensus document	11 Authors	SCAI	Expert consensus based on information from previous guidelines/expert consensus documents	NR	Expert consensus

ACC(F) – American College of Cardiology (Foundation); AHA – American Heart Association; AMA – American Medical Association; API – Association of Physicians of India; BCIS – British Cardiovascular Intervention society; BCS – British Cardiovascular Society; CCN – Cardiac Care Network of Ontario; CCS – Canadian Cardiovascular Society; CSANZ – Cardiac Society of Australia and New Zealand; DGK – German Cardiac Society; EACTS – European Association for Cardio-Thoracic Surgery; ESC – European Society of Cardiology; GISE – Italian Group of Hemodynamic Studies; JCS – Japanese circulation Society; NR – not reported; NVVC – Netherlands Association of Cardiology; PTK – Polish Cardiac Society; RCSI – Royal College of Surgeons in Ireland; SCAI – the Society for Cardiovascular Angiography and Interventions; SICI – Italian Society of Invasive Cardiology; SSC – Swiss Society of Cardiology.

*Levels of evidence: Level A: evidence demonstrated by more than one randomized clinical study or meta-analyses; Level B: evidence demonstrated by a randomized clinical study or multicenter, large-scale registry studies; Level C: evidence represents consensus opinion of experts, small-scale clinical studies, results of sub-analysis, and/or others

Classes of recommendations: Class I: evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; Class II: conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; Class IIa: weight of evidence/opinion is in favour of usefulness/efficacy; Class IIb: usefulness/efficacy is less well established by evidence/opinion; Class III: evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table A.10: Table of characteristics and outcomes for RQ3

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
Adogwa (2009)[288] **US** **Cross-sectional study**	**Total population (patients/procedures):** 75,869 **Population(s) of interest:** Total PCI, emergent cases in patients > 65 years old. **Study period:** 2000-2005 **Age:** 55-64 years old: 48.7%, ≥ 65 years old: 22.2% **Male:** 62.6% **Stent usage:** NR **Emergent cases:** 40.7% (High-volume hospital = 39.4%, Low-volume hospital = 49.4%) **Number of hospitals:** 30	**<u>High-volume hospital:</u>** **Population:** 57,249 (75.5%) **Definition:** ≥500 PCI procedures per year **<u>Low-volume hospital:</u>** **Population** 6,006 (7.9%) **Definition:** <250 PCI procedures per year **Lower bound:** 12 PCI procedures per year **Mean PCI volume per LVH per year:** 75.1	**Database:** Kentucky Hospital discharge database **Datatype:** Administrative **Risk adjustment:** Age, Sex, Severity, Comorbidity **Number of groupings:** 3 **Level of analysis:** (Hospital*)	**<u>Primary:</u>** **In-hospital mortality rates:** NR **Adjusted OR (95% CI) of in-hospital mortality:** 1.42 (1.13-1.78) [Low vs. Medium] [Medium = reference]

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
Arora (2016)[289] **US** **Cross-sectional**	**Total population (patients/procedures):** 107,849 **Population(s) of interest:** Multi-vessel PCI **Study period:** 2006-2011 **Age:** 65-79 years olds: 23.9% ≥ 80 years old: 11.7% **Male:** 67.9% **Stent usage:** 100% **Emergent cases:** 66.9%*** (Also includes urgent) **Number of hospitals:** NR	**<u>High-volume hospital:</u>** **Population:** 27,000 approx. (25%) **Definition:** ≥1167 PCI procedures per year **<u>Low-volume hospital:</u>** **Population** 27,000 approx. (25%) **Definition:** <353 PCI procedures per year **Lower bound:** 5 PCI procedures per year **Mean PCI volume per LVH per year:** NR	**Database:** National Inpatient Sample **Datatype:** Administrative **Risk adjustment:** Age, Sex, Severity, Comorbidity, Hospital characteristics, Clustering, Treatment differences **Number of groupings:** 4 **Level of analysis:** (Hospital*)	**<u>Primary:</u>** **In-hospital mortality rates in MVPCI:** Overall = 0.7% **Adjusted OR (95% CI) of in-hospital mortality in MVPCI:** 0.75 (0.56-0.99) **<u>Secondary:</u>** **Adjusted OR (95% CI) of composite of in-hospital mortality and peri-procedural complications in MVPCI** 0.91 (0.80-1.05) **Adjusted OR (95% CI) of length of stay in MVPCI:** -0.31 days (-0.42 to -0.20)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
Badheka (2014)[290] **US** **Cross-sectional**	**Total population (patients/procedures):** 457,498 **Population(s) of interest:** Total PCI, Multi-vessel PCI, MI, Shock **Study period:** 2005-2009 **Age:** Mean ± SD: 64.5 ± 0.01 **Male:** 66.21% **Stent usage:** 100% **Emergent cases:** 67% (High-volume hospital = 64.2%, Low-volume hospital = 71.6%, High-volume operator = 55.4%, Low-volume operator = 82.3%) **Number of hospitals:** NR **Number of operators:** NR	**<u>High-volume hospital:</u>** **Population:** 114,244 (24.97%) **Definition:** > 1641 PCI procedures per year **<u>Low-volume hospital:</u>** **Population** 114,569 (25.04%) **Definition:** ≤ 542 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVH per year:** NR **<u>High-volume operator:</u>** **Population:** 114,011 (24.92%) **Definition:**	**Database:** National Inpatient Sample **Datatype:** Administrative **Risk adjustment:** Age, Sex, Severity, Comorbidity, Hospital characteristics, Clustering, Treatment differences **Number of groupings:** 4 **Level of analysis:** Hospital and Operator	**<u>Primary:</u>** **In-hospital mortality rates:** Overall = 1.08% HVH = 0.68% LVH = 1.54% HVO = 0.59% LVO = 0.68% **Adjusted OR (95% CI) of in-hospital mortality:** Hospital: 0.88 (0.75-1.04 Operator: 0.65 (0.58-0.73) **Adjusted OR (95% CI) of in-hospital mortality, in emergent/urgent subgroup:** Hospital: NR Operator: 0.70 (0.62–0.78) **Adjusted OR (95% CI) of in-hospital mortality, in MI subgroup:** Hospital: NR Operator: 0.69 (0.59–0.80 **Adjusted OR (95% CI) of in-hospital mortality, in Shock subgroup:** Hospital: NR Operator: 0.79 (0.66–0.93) **Adjusted OR (95% CI) of in-hospital mortality, in MVPCI subgroup:** Hospital: NR Operator: 0.80 (0.62–1.05)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
		>100 PCI procedures per year **<u>Low-volume operator:</u>** **Population** 115,813 (25.3%) **Definition:** ≤ 15 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVO per year:** NR		**<u>Secondary:</u>** **Adjusted OR (95% CI) of composite of in-hospital mortality or any complication** Hospital: 1.02 (0.93 –1.12) Operator: 0.61 (0.58–0.63) **Adjusted OR (95% CI) of log scale of length of stay:** Hospital: 0.95 (0.94–0.96 Operator: 0.95 (0.94–0.95)
Barnett (2018)[291] **US** **Retrospective cohort study**	**Total population (patients/procedures):** 13,237 **Population(s) of interest:** Elective PCI **Study period:** 2008-2011 **Age:** Mean ± SD: 59.3 ± 5.1	**<u>High-volume hospital:</u>** **Population:** 8,767 (66.2%) **Definition:** ≥ 200 PCI procedures per year **<u>Low-volume hospital:</u>** **Population**	**Database:** Community Care Claims Data and the VA electronic medical records **Datatype:** Administrative **Risk adjustment:** Age, Sex, Severity, Comorbidity,	**<u>Primary:</u>** **30-day mortality rate in elective subgroup:** High volume = 1.17% Low volume = 0.84% **Adjusted RR (95% CI) of 30-day mortality in elective subgroup:** 0.69 (0.41-1.19) [Low vs High] [High = reference] **<u>Secondary:</u>** **Adjusted RR (95% CI) of 30-day re-admission:** 0.90 (0.73-1.11) [Low vs High] [High = reference]

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Male: 97.9% **Stent usage:** NR **Emergent cases:** 0% **Number of hospitals:** NR	4,470 (33.8%) **Definition:** < 200 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVH per year:** NR	Clustering, Treatment differences **Number of groupings:** 2 **Level of analysis:** (Hospital*)	
Fanaroff (2017)[292] **US** **Cross-sectional**	**Total population (patients/procedures):** 3,747,866 **Population(s) of interest:** Total PCI, STEMI, NSTEMI/UA **Study period:** 2009-2015 **Age:** Median (IQR): 65 (56–74) **Male:** 68.1% **Stent usage:** 73.5%*** (DES only)	**<u>High-volume hospital:</u>** **Population:** NR **Definition:** > 800 PCI procedures per year **<u>Low-volume hospital:</u>** **Population** NR **Definition:** < 400 PCI procedures per year **Lower bound:** NR	**Database:** NCDR - CathPCI **Datatype:** Clinical **Risk adjustment:** Age, Severity, Comorbidity, Clustering, Treatment differences **Number of groupings:** 3 **Level of analysis:** (Hospital*) and Operator	**<u>Primary:</u>** **In-hospital mortality rates:** Overall = 1.6% HVO = 1.48% LVO = 1.86% **Adjusted OR (95% CI) of in-hospital mortality:** 0.86 (0.83-0.89) **Adjusted OR (95% CI) of in-hospital mortality in STEMI subgroup:** 1.13 (1.08-1.19) [high vs. low][high = reference] **Adjusted OR (95% CI) of in-hospital mortality in NSTEMI/UA subgroup:** 1.20 (1.13-1.28) [high vs. low][high = reference] **<u>Secondary:</u>**

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Emergent cases: 18.3% (High-volume operator = 16.6%, Low-volume operator = 22.6%) **Number of hospitals:** 1,584 **Number of operators:** 10,496	**Mean PCI volume per LVH per year:** NR **<u>High volume operator:</u>** **Population:** 2,338,913 (62.4%) **Definition:** > 100 PCI procedures per year **<u>Low volume operator:</u>** **Population** 371,861 (10%) **Definition:** < 50 PCI procedures per year **Lower bound:** 1 PCI procedure per year **Mean PCI volume per LVO per year:** 14		**Adjusted OR (95% CI) of bleeding:** 1.00 (0.96-1.05) [high vs. low][high = reference] **Adjusted OR (95% CI) of requirement for dialysis:** 1.09 (1.01-1.17) [high vs. low][high = reference]

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
Fanaroff (2018)[293] **US** **Cross-sectional**	**Total population (patients/procedures):** 723,644 **Population(s) of interest:** Total PCI, STEMI, NSTEMI/UA, CTO, LM PCI **Study period:** 2009-2014 **Age:** Median (IQR): 74 (69-80) **Male:** 62% **Stent usage:** 70.5%***(DES only) **Emergent cases:** 14.5% (High-volume operator = 13.2%, Low-volume operator = 17.1%) **Number of hospitals:** NR **Number of operators:** 8,936	**<u>High-volume operator:</u>** **Population:** 437,977 (60.5%) **Definition:** > 100 PCI procedures per year **<u>Low-volume operator:</u>** **Population** 74,721 (10.3%) **Definition:** < 50 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVO per year:** 3.9	**Database:** NCDR CathPCI linked with Medicare claims data **Datatype:** Clinical and administrative **Risk adjustment:** Age, Severity, Comorbidity, Clustering, Treatment differences **Number of groupings:** 3 **Level of analysis:** (Operator)*	**<u>Primary:</u>** **In-hospital mortality rates:** Overall = 2.4% HVO = 2.0% LVO = 2.4% **30 days mortality rates:** Overall = 3.3% HVO = 3.2% LVO = 3.5% **1 year mortality rates:** Overall = 9.6% HVO = 9.8% LVO = 9.5% **Adjusted OR (95% CI) of in-hospital mortality:** 0.79 (0.75–0.83) **Adjusted OR (95% CI) of 30-day mortality:** 0.91 (0.86-0.96) **Adjusted HR (95% CI) of 1 year mortality:** 1.04 (1.00-1.08)] **Adjusted HR (95% CI) of in-hospital mortality in STEMI subgroup:** 0.87 (0.82–0.92) **Adjusted HR (95% CI) of in-hospital mortality in NSTEMI/UA subgroup:** 0.87 (0.80–0.95)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
				Adjusted HR (95% CI) of 30-day mortality in STEMI subgroup: 0.86 (0.79-0.92) **Adjusted HR (95% CI) of 30-day mortality in NSTEMI/UA subgroup:** 0.97 (0.91-1.05) **Adjusted HR (95% CI) of 1 year mortality in STEMI subgroup:** 1.01 (0.94–1.09) **Adjusted HR (95% CI) of 1 year mortality in NSTEMI/UA subgroup:** 1.04 (1.00–1.09) **Adjusted HR (95% CI) of in-hospital mortality in CTO:** 0.71 (0.60-0.86) **Adjusted HR (95% CI) of 30-day mortality in CTO:** NR **Adjusted HR (95% CI) of 1 year mortality in CTO:** 1.10 (0.93-1.31 **Adjusted HR (95% CI) of in-hospital mortality in LMPCI:** 0.73 (0.60-0.89) **Adjusted HR (95% CI) of 30-day mortality in LMPCI:**

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
				NR **Adjusted HR (95% CI) of 1 year mortality in LMPCI:** 1.01 (0.84-1.22) **<u>Secondary:</u>** **Adjusted OR (95% CI) of major bleeding at 30 days:** OR 0.96 (0.91-1.12) **Adjusted HR (95% CI) of MACE at 1 year:** 1.01 (0.99–1.04) **Adjusted HR (95% CI) of recurrent MI at 1 year:** 0.98 (0.95-1.02) **Adjusted HR (95% CI) of unplanned revascularisation at 1 year:** 1.03 (0.99-1.06)
Hulme (2018)[271] **UK (England and Wales)** **Retrospective cohort study**	**Total population (patients/procedures):** 133,970 **Population(s) of interest:** Total PCI, ACS patients, Primary PCI patients **Study period:** 2013-2014 **Age:**	**<u>High-volume operator:</u>** **Population:** 129,843 (96.9%) **Definition:** ≥ 75 PCI procedures per year **<u>Low-volume operator:</u>** **Population:**	**Database:** BCIS registry with NHS linkage **Datatype:** Clinical and administrative **Risk adjustment:** Age, Sex, Severity, Comorbidity, Hospital characteristics,	**<u>Primary:</u>** **In-hospital mortality rates:** NR **30-day mortality rates:** Overall = 2.6% HVO = 2.5% LVO = 2.9% **Adjusted OR (95% CI) of in-hospital mortality, for total PCI:** 1.00 (0.76-1.32)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Mean ± SD: 65.1 ± 12.1 **Male:** 74.3% **Stent usage:** 92.2% **Emergent cases:** 27.6%***(STEMI cases) **Number of hospitals:** 84 **Number of operators:** 540	4,127 (3.1%) **Definition:** < 75 PCI procedures per year **Lower bound:** 0 PCI procedures per year **Mean PCI volume per LVO per year:** 18	Clustering, Treatment differences **Number of groupings:** 2 **Level of analysis:** Operator	**Adjusted OR (95% CI) of 30-day mortality, for total PCI:** 0.96 (0.79-1.18) **Adjusted OR (95% CI) of in-hospital mortality in primary PCI subgroup:** 0.88 (0.65-1.22) **Adjusted OR (95% CI) of 30-day mortality in primary PCI subgroup:** 0.93 (0.72-1.22) **Adjusted OR (95% CI) of in-hospital mortality in ACS subgroup:** 1.01 (0.76–1.34) [high vs. low] [high = reference] **Adjusted OR (95% CI) of 30-day mortality in ACS subgroup:** 1.09 (0.88-1.35) [high vs. low] [high = reference] **<u>Secondary:</u>** **Adjusted OR (95% CI) for MACE, for total PCI:** 1.13 (0.92–1.38) [high vs. low] [high = reference] **Adjusted OR (95% CI) for MACE, for Primary PCI:** 1.24 (0.95–1.61) [high vs. low] [high = reference]

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
Inohara (2017)[299] **Japan** **Cross-sectional**	**Total population (patients/procedures):** 323,322 **Population(s) of interest:** Total PCI, emergent/urgent cases **Study period:** 2014-2015 **Age:** Mean ± SD: 70.0 ± 11.0 **Male:** 76% **Stent usage:** NR **Emergent cases:** 27.7% **Number of hospitals:** 625 **Number of operators:** 4211	**High-volume hospital:** **Population:** NR **Definition:** ≥ 778 PCI procedures per year **Low-volume hospital:** **Population:** NR **Definition:** ≤ 149 PCI procedures per year **Lower bound:** 10 PCI procedures per year **Mean PCI volume per LVH per year:** NR **High-volume operator:** **Population:** NR **Definition:** ≥ 134 PCI procedures	**Database:** J-PCI **Datatype:** Clinical **Risk adjustment:** Age, Sex, Severity, Comorbidity **Number of groupings:** 10 **Level of analysis:** Hospital and Operator	**Primary:** **In-Hospital mortality rates:** Overall = 0.9% HVH= 0.4% LVH= 1.3% HVO = 0.6% LVO = 1.1% **Adjusted OR (95% CI) of in-hospital mortality:** Hospital: 0.47 (0.38-0.57) Operator: 1.03 (0.84-1.25) **Adjusted OR (95% CI) of in-hospital mortality, for emergent/urgent subgroup:** Hospital: 0.5 (0.4-0.63) Operator: 1.13 (0.91-1.39) **Secondary:** **Adjusted OR (95% CI) for composite of in-hospital death and complications:** Hospital: 0.49 (0.43-0.56 Operator: 1.0 (0.89-1.13)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
		per year **<u>Low-volume operator:</u>** **Population:** NR **Definition:** ≤ 23 PCI procedures per year **Lower bound:** 1 PCI procedure per year **Mean PCI volume per LVO per year:** NR		
Kim (2013)[304] **South Korea** **Retrospective cohort study**	**Total population (patients/procedures):** 44,363 **Population(s) of interest:** Total PCI **Study period:** 2003-2004 **Age:** Mean age ± SD: 63.8 ± 10.2 **Male:**	**<u>High-volume hospital:</u>** **Population:** 9,071 (20.5%) **Definition:** ≥ 400 PCI procedures per year **<u>Low-volume hospital:</u>** **Population:** 19,669 (44.3%)	**Database:** Korea National Health Insurance Review & Assessment Service and Korean National Statistical Office **Datatype:** Administrative **Risk adjustment:** Age, Sex, Severity, Comorbidity, Treatment differences	**<u>Primary</u>** **30-day mortality rates:** Overall = 1.1% HVH = 1.0% LVH =1.4% **Adjusted OR (95% CI) of 30-day mortality:** 0.65 (0.49-0.85)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	64.9% **Stent usage:** 60.9% **Emergent cases:** 39.7% **Number of hospitals:** 102 **Number of operators:** NR	**Definition:** < 200 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVH per year:** 151.2	**Number of groupings:** 3 **Level of analysis:** Hospital	
Kodaira (2018)[298] **Japan** **Cross-sectional**	**Total population (patients/procedures):** 14,437 **Population(s) of interest:** Total PCI, STEMI, CTO lesion, Type C lesion and bifurcation lesion **Study period:** 2010-2015 **Age:** Mean ± SD: 67.7 ± 11.1 **Male:** 79.6% **Stent usage:**	**<u>High-volume hospital:</u>** **Population:** 11,602 (80.4%) **Definition:** ≥ 200 PCI procedures per year **<u>Low-volume hospital:</u>** **Population:** 2,835 (19.6%) **Definition:** < 200 PCI procedures per year **Lower bound:**	**Database:** Japan Cardiovascular Database–Keio inter-hospital Cardiovascular Studies PCI registry **Datatype:** Clinical **Risk adjustment:** Age, Severity, Comorbidity, Clustering **Number of groupings:** 2	**<u>Primary</u>** **In-hospital mortality rates:** Overall = 1.2% HVH = 1.2% LVH = 1.3% **Adjusted OR (95% CI) of in-hospital mortality:** 1.02 (0.89-1.17) [high vs. low] [low = reference] **Adjusted OR (95% CI) of in-hospital mortality, for STEMI subgroup:** 1.42 (0.85-2.37) **Adjusted OR (95% CI) of in-hospital mortality, for CTO subgroup:** 1.10 (0.71-1.69) **Adjusted OR (95% CI) of in-hospital mortality,**

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	69.1%*** (DES only) **Emergent cases:** 19.2%*** (STEMI only) (High-volume hospital = 18.5%, Low-volume hospital = 22.2%) **Number of hospitals:** 14 **Number of operators:** NR	NR **Mean PCI volume per LVH per year:** 85.9	**Level of analysis:** Hospital	**for Type C subgroup:** 1.00 (0.86-1.15) **Adjusted OR (95% CI) of in-hospital mortality, for bifurcation subgroup:** 1.02 (0.85-1.22) **Secondary** **Adjusted OR (95% CI) of in-hospital general complications:** 1.433 (0.954 - 2.152)
Kontos (2013)[294] **US** **Cross-sectional**	**Total population (patients/procedures):** 87,324 **Population(s) of interest:** Primary PCI, shock **Study period:** 2006-2009 **Age:** > 70 years old: 24.2% **Male:** 71.7% **Stent usage:** NR **Emergent cases:** 100%	**High-volume hospital:** **Population:** 47,450 (54.3%) **Definition:** > 60 Primary PCI procedures per year **Low-volume hospital:** **Population:** 13267 (15.2%) **Definition:** ≤ 36 Primary PCI Procedures per year	**Database:** NCDR - CathPCI **Datatype:** Clinical **Risk adjustment:** Age, Severity, Comorbidity, Treatment differences, (Hospital characteristics)** **Number of groupings:** 3 **Level of analysis:** Hospital	**Primary** **In-hospital mortality rates:** Overall = 4.9% HVH = 4.8% LVH = 5.6% **Adjusted OR (95% CI) of in-hospital mortality:** 0.82 (0.74-0.91) **Adjusted OR (95% CI) of in-hospital mortality, for shock subgroup:** 1.14 (0.98–1.32)] **Secondary:** **Adjusted RR (95% CI) of achieving Door to Balloon Time of < 90 mins:** 0.93 (0.89–0.96)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Number of hospitals: 738 **Number of operators:** NR	**Lower bound:** 5 Primary PCI procedures per year **Mean PCI volume per LVH per year:** 15.9		
Kubo (2019)[302] **Japan** **Cross-sectional**	**Total population (patients/procedures):** 17,549 **Population(s) of Interest:** ACS patients with Cardiogenic Shock **Study period:** 2014-2016 **Age:** Mean ± SD: 70.8 ±12.4 **Male:** 74% **Stent usage:** NR **Emergent cases:** 100% **Number of hospitals:**	**<u>High volume hospital:</u>** **Population:** 2,783 (15.9%) **Definition:** > 1,490 cases per 3 years **<u>Low volume hospital:</u>** **Population:** 4,970 (28.3%) **Definition:** <640 cases per 3 years **Lower bound:** NR **Mean PCI volume per LVH per year:** NR	**Database:** J-PCI **Datatype:** Clinical **Risk adjustment:** Age, Sex, Comorbidity, Severity, Treatment differences **Number of groupings:** 4 **Level of analysis:** Hospital	**<u>Primary:</u>** **In-hospital mortality rates in Cardiogenic Shock patients:** Overall = 13.2% HVH =12.3% LVH = 14.2% **Adjusted OR (95% CI) of in-hospital mortality Cardiogenic Shock patients:** 0.68 (0.50-0.93) **<u>Secondary:</u>** **Adjusted OR (95% CI) of access site bleeding in Cardiogenic Shock patients:** 0.69 (0.47-0.99) **Adjusted OR (95% CI) of non-access site bleeding in Cardiogenic Shock patients:** 0.78 (0.49-1.25)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	1,019 **Number of operators:** NR			
Kumbhani (2009)[295] **US** **Cross-sectional**	**Total population (patients/procedures):** 29,513 **Population(s) of interest:** Primary PCI, total PCI, STEMI **Study period:** 2001-2007 **Age:** Mean ± SD: 60.8 ± 13.1 **Male:** 71.4% **Stent usage:** NR **Emergent cases:** 100% **Number of hospitals:** 166 **Number of operators:** NR	**<u>High-volume hospital:</u>** **Population:** 16,605 (56.3%) **Definition:** > 70 Primary PCI procedures per year (Total PCI > 400 PCI procedures per year) **<u>Low-volume hospital:</u>** **Population:** 3,900 (13.2%) **Definition:** ≤ 36 Primary PCI Procedures per year (Total PCI: < 200 PCI procedures per year) **Lower bound:** 9 Primary PCI procedures per year (39 total PCI procedures per year)	**Database:** American Heart Association's Get With the Guidelines registry **Datatype:** Clinical **Risk adjustment:** Age, Sex, Comorbidity, Clustering, Hospital characteristics, (Treatment differences)** **Number of groupings:** 3 **Level of analysis:** Hospital	**<u>Primary</u>** **In-hospital mortality rates:** Overall = 3.2% HVH = 3.0% LVH = 3.9% **Adjusted OR (95% CI) of in-hospital mortality, for total PCI:** 0.83 (0.57-1.22) **Adjusted OR (95% CI) of in-hospital mortality, for primary PCI:** 0.77 (0.53-1.10) **Adjusted OR (95% CI) of in-hospital mortality, STEMI subgroup:** 1.52 (1.16-2.00) [high vs. low] [high = reference] **<u>Secondary:</u>** **Adjusted OR (95% CI) of achieving door-to-balloon time of < 90 mins:** 0.72 (0.54-0.96) [high vs. low] [high = reference]

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
		Mean PCI volume per LVH per year: 10.3 Primary PCI (NR for total PCI)		
Kuwabara (2011)[300] **Japan** **Cross-sectional**	**Total population (patients/procedures):** 8,391 **Population(s) of interest:** Primary PCI **Study period:** 2006 **Age:** Mean ± SD: 67.0 ± 12.1 **Male:** 75.8% **Stent usage:** 84.2% **Emergent cases:** 94% (High-volume hospital = 94.8%, low-volume hospital = 90.6%) **Number of hospitals:** 303	**High-volume hospital:** **Population:** 4,042 (48.2%) **Definition:** ≥ 78 primary PCI procedures per year **Low-volume hospital:** **Population:** 776 (9%) **Definition:** ≤ 26 Primary PCI procedures per year **Lower bound:** 6 Primary PCI procedures per year **Mean PCI volume per LVH per year:** 18.7 Primary PCI	**Database:** Japanese Diagnosis Procedure Combination study group dataset **Datatype:** Administrative **Risk adjustment:** Age, Sex, Severity, Comorbidity, Clustering, Treatment differences **Number of groupings:** 4 **Level of analysis:** Hospital	**Primary** **In-hospital mortality rates:** Overall = 5.2% HVH = 4.9% LVH = 7.0% **Adjusted OR (95% CI) of in-hospital mortality:** 0.66 (0.47-0.93)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Number of operators: NR			
Navarese (2011)[305] **Italy** **Cross-sectional**	**Total population (patients/procedures):** 2,558 **Population(s) of interest:** Primary PCI **Study period:** 2005-2006 **Age:** Median age between 59 and 64 **Male:** 77.8% **Stent usage:** NR **Emergent cases:** 100% **Number of hospitals:** 30 **Number of operators:** NR	**<u>High-volume hospital:</u>** **Population:** NR **Definition:** > 66 Primary PCI procedures per year (if time-to-presentation ≤ 90 minutes) **<u>Low-volume hospital:</u>** **Population:** NR **Definition:** ≤ 66 Primary PCI procedures per year (if time-to-presentation ≤ 90 minutes) **Lower bound:** NR **Mean PCI volume per LVH per year:**	**Database:** LombardIMA registry **Datatype:** Clinical **Risk adjustment:** Age, Sex, Severity, Comorbidity, Clustering, Hospital characteristics **Number of groupings:** 2 **Level of analysis:** Hospital	**<u>Primary</u>** **In-hospital mortality rates:** Overall = NR HVH = NR LVH = NR **Adjusted OR (95% CI) of in-hospital mortality, if time to presentation is ≤ 90 mins:** 0.21 (0.10-0.47) **Adjusted OR (95% CI) of in-hospital mortality, if time to presentation is 90-180 mins:** 0.55 (0.31-0.99)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
		NR		
O'Neill (2017)[303] **UK (England and Wales)** **Retrospective cohort study**	**Total population (patients/procedures):** 427,467 **Population(s) of interest:** Total PCI, primary PCI, elective PCI **Study period:** 2007-2013 **Age:** Mean ± SD: 64.9 ± 11.9 **Male:** 73.5% **Stent usage:** 92% **Emergent cases:** 26.6% (High-volume hospital = 28.2%, low-volume hospital = 26.4%) **Number of hospitals:** 93	**<u>High-volume hospital:</u>** **Population:** 95,115 (22.3%) [Primary PCI 23,441 (24.9%)] **Definition:** ≥ 2,000 PCI procedures per year **<u>Low-volume hospital:</u>** **Population:** 2,588 (0.6%) [Primary PCI 69 (0.07%)] **Definition:** ≤ 199 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVH per year:** 73.9 total PCI	**Database:** BCIS registry with NHS linkage **Datatype:** Clinical and administrative **Risk adjustment:** Age, Sex, Severity, Comorbidity, Clustering **Number of groupings:** 6 **Level of analysis:** Hospital	**<u>Primary</u>** **30-day mortality rates:** Overall = 1.9% (4.8% primary) HVH = NR LVH = NR **Adjusted OR (95% CI) of 30-day mortality, for total PCI:** 1.10 (0.85-1.44) **Adjusted OR (95% CI) of 30-day mortality, for primary PCI:** 0.98 (0.85-1.11) **Adjusted OR (95% CI) of 30-day mortality, for elective subgroup:** Not reported as Odds Ratio, but graphically not significant.

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Number of operators: NR	procedures per year (2.5 Primary PCI procedures per year)		
Qian (2019)[297] **US** **Cross-sectional**	**Total population (patients/procedures):** 144,196 **Population(s) of Interest:** Total PCI, STEMI, Patients without STEMI **Study period:** 2012-2015 **Age:** Less than 50 years 9.22% 50-59 years 23.10% 60-69 years old: 30.8% 70-79 years old: 24.3% ≥ 80 years old: 12.5% **Male:** 70.3% **Stent usage:** NR **Emergent cases:** 11.8% *** (STEMI only)	**<u>High volume hospital:</u>** **Population:** 141,153 (97.9%) **Definition:** ≥ 200 PCI procedures per year **<u>Low volume hospital:</u>** **Population:** 3,043 (2.1%) **Definition:** <200 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVH per year:** 101.4 **<u>High volume operator:</u>**	**Database:** New York State PCI Registry **Datatype:** Clinical **Risk adjustment:** Age, Severity, Comorbidity, Clustering **Number of groupings:** 2 **Level of analysis:** Hospital and Operator	**30-day mortality rates:** Overall = 1.15% HVH = NR LVH = NR HVO = NR LVO = NR **Adjusted OR (95% CI) of 30-day mortality:** Hospital: 1.15 (0.88-1.51) Operator: 0.89 (0.70-1.12) **Adjusted OR (95% CI) of 30-day mortality, STEMI subgroup:** Hospital (36 STEMI PCI threshold): 0.61 (0.22-1.73) Operator (11 STEMI PCI threshold): 1.15 (0.85-1.56) **Adjusted OR (95% CI) of 30-day mortality, patients without STEMI subgroup:** Hospital: 1.02 (0.66-1.56) Operator: 0.93 (0.68-1.27)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Number of hospitals: 63 **Number of operators:** 458	**Population:** 137,247 (95.2%) **Definition:** ≥ 50 PCI procedures per year **<u>Low volume operator:</u>** **Population:** 6,949 (4.8%) **Definition:** < 50 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVO per year:** 17.5		
Shiraishi (2008)[301] **Japan** **Cross-sectional**	**Total population (patients/procedures):** 1,785 **Population(s) of interest:** Primary PCI **Study period:** 2000-2005 **Age:**	**<u>High-volume hospital:</u>** **Population:** 764 (42.8%) **Definition:** > 36 Primary PCI per year **<u>Low-volume hospital:</u>**	**Database:** AMI-Kyoto Multi-Center Risk Study Group **Datatype:** Clinical **Risk adjustment:** Age, Sex, Severity, Comorbidity,	**<u>Primary</u>** **In-hospital mortality rates:** Overall = 10.1% HVH = 10.5% LVH = 9.9% **Adjusted OR (95% CI) of in-hospital mortality:** 1.24 (0.86-1.80)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Mean ± SD: 67.8 ± 12.3 **Male:** 73.6% **Stent usage:** 78.1% **Emergent cases:** 100% **Number of hospitals:** 16 **Number of operators:** NR	**Population:** 1021 (57.2%) **Definition:** < 36 Primary PCI per year **Lower bound:** 3 Primary PCI procedures per year **Mean PCI volume per LVH per year:** 13.1 Primary PCI procedures per year	Treatment differences **Number of groupings:** 2 **Level of analysis:** Hospital	
Srinivas (2009)[296] **US** **Cross-sectional**	**Total population (patients/procedures):** 7,321 **Population(s) of interest:** Primary PCI **Study period:** 2000-2002 **Age:** Mean ± SD: 61.2 ± 13.0 **Male:** 71.4%	**<u>High-volume hospital:</u>** **Population:** 6,173 (84.3%) **Definition:** >50 Primary PCI procedures per year **<u>Low-volume hospital:</u>** **Population:** 1,148 (15.7%) **Definition:** ≤ 50 Primary PCI	**Database:** New York State PCI registry **Datatype:** Clinical **Risk adjustment:** Age, Sex, Severity, Comorbidity **Number of groupings:** 2 **Level of analysis:** Hospital and Operator	**<u>Primary</u>** **In-hospital mortality rates:** Overall = 3.7% HVH = 3.4% LVH = 5.4% HVO=3.3% LVO=4.9 **Adjusted OR (95% CI) of in-hospital mortality:** Hospital at threshold of 50 PCI /year: 0.58 (0.38-0.88) Operator at threshold of 10 PCI/year: 0.66 (0.48-0.92)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Stent usage: 90.9% **Emergent cases:** 100% **Number of hospitals:** 41 **Number of operators:** 266	procedures per year **Lower bound:** 1 Primary PCI procedure per year **Mean PCI volume per LVH per year:** 21.3 Primary PCI procedures per year **<u>High-volume operator:</u>** **Population:** 5,238 (71.5%) **Definition:** > 10 Primary PCI procedures per year **<u>Low-volume operator:</u>** **Population:** 2,083 (28.5%) **Definition:** ≤ 10 Primary PCI procedures per year **Lower bound:** NR		

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
		Mean PCI volume per LVO per year: 4 Primary PCI procedures per year		
Xu (2016)[306] **China** **Prospective cohort study**	**Total population (patients/procedures):** 1,948 **Population(s) of Interest:** LM PCI **Study period:** 2004-2011 **Age:** Mean ± SD: 59.9 ± 10.5 **Male:** 78.9% **Stent usage:** 85.9% **Emergent cases:** NR **Number of hospitals:** 1	**<u>High-volume operator:</u>** **Population:** 1,422 (73.0%) **Definition:** ≥ 15 LM PCI Procedures per year for 3 consecutive years **<u>Low-volume operator:</u>** **Population:** 526 (27.0%) **Definition:** < 15 LM PCI Procedures per year for 3 consecutive years **Lower bound:** 1 LM PCI procedure per year **Mean PCI volume**	**Database:** Fu Wai Hospital, China **Datatype:** Clinical **Risk adjustment:** Age, Severity, Comorbidity, Treatment differences **Number of groupings:** 2 **Level of analysis:** (Operator)*	**<u>Primary</u>** **30-day mortality rates in LMPCI:** Overall = 1.0% HVO = 0.6% LVO = 2.1% **1 year mortality rates in LMPCI:** Overall = 2.2% HVO = 1.8% LVO = 3.2% **3 year mortality rates in LMPCI:** Overall = 4.2% HVO = 3.8% LVO = 5.3% **Adjusted HR (95% CI) of 30-day all-cause mortality in LMPCI:** 0.30 (0.12–0.73) **Adjusted HR (95% CI) of 3-year all-cause mortality in LMPCI:** 0.70 (0.45–1.11) **<u>Secondary</u>**

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Number of operators: 25	**per LVO per year:** 3.7 LM PCI procedures per year		**Adjusted HR (95% CI) of 30-day MI in LMPCI:** 0.72 (0.48–1.09) **Adjusted HR (95% CI) of 3 years MI in LMPCI:** 0.86 (0.59–1.26) **Adjusted HR (95% CI) of 30-day target vessel revascularization in LMPCI:** 1.79 (0.51–6.21) **Adjusted HR (95% CI) of 3 year target vessel revascularization in LMPCI:** 1.30 (0.84–2.01) **Adjusted HR (95% CI) of 30-day composite of mortality or stroke in LMPCI** 0.70 (0.47–1.05) **Adjusted HR (95% CI) of 3 year composite of mortality or stroke in LMPCI:** 0.78 (0.57–1.07)
Yu (2017)[307] **Taiwan** **Cross-sectional**	**Total population (patients/procedures):** 34,193 **Population(s) of interest:** Total PCI **Study period:** 2009 **Age:**	**High-volume hospital:** **Population:** 30,515 (89.2%) **Definition:** ≥ 200 PCI procedures per year **Low-volume hospital:**	**Database:** Taiwan National Health Insurance Research Database **Datatype:** Administrative **Risk adjustment:** Age, Comorbidity, Treatment differences,	**Primary** **30-day mortality rates:** Overall = NR **Adjusted OR (95% CI) of 30-day mortality:** Hospital: 1.10 (0.84-1.43) Operator: 0.43 (0.35-0.52)

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Mean ± SD: 65.73 ± 12.24 **Male:** 73.4% **Stent usage:** 67% **Emergent cases:** NR **Number of hospitals:** 79 **Number of operators:** 1,318	**Population:** 3,678 (10.8%) **Definition:** < 200 PCI procedures per year **Lower bound:** NR **Mean PCI volume per LVH per year:** NR **<u>High-volume operator:</u>** **Population:** 25,062 (74.3%) **Definition:** ≥ 50 PCI procedures per year **<u>Low-volume operator:</u>** **Population:** 9,131 (26.7%) **Definition:** < 50 PCI procedures per year	Hospital characteristics, (Clustering)** **Number of groupings:** 2 **Level of analysis:** Hospital and Operator	

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
		Lower bound: NR **Mean PCI volume per LVO per year:** NR		
Zahn (2008)[308] **Germany** **Cross-sectional**	**Total population (patients/procedures):** 27,965 **Population(s) of interest:** Total PCI, STEMI/NSTEMI patients **Study period:** 2003 **Age:** Mean ± SD: 65.7 ± 11.1 **Male:** 72.9% **Stent usage:** 81.4% **Emergent cases:** 22.5%*** (STEMI only) (High volume hospital = 22.3%, Low volume hospital = 23.5%)	**<u>High-volume hospital:</u>** **Population:** 22,211 (79.4%) **Definition:** > 325 PCI procedures per year **<u>Low-volume hospital:</u>** **Population:** 5,754 (20.6%) **Definition:** < 325 PCI procedures per year **Lower bound:** 4 PCI procedures per year **Mean PCI volume per LVH per year:** NR	**Database:** ALKK PCI registry **Datatype:** Clinical **Risk adjustment:** Age, Sex, Severity, Comorbidity, (Clustering)** **Number of groupings:** 2 **Level of analysis:** Hospital	**<u>Primary</u>** **In-hospital mortality rates:** Overall = 1.4% HVH = 1.2% LVH = 1.9% **Adjusted OR (95% CI) of in-hospital mortality:** 0.67 (0.52-0.87

First author (year) Country Study design	Population demographics	High- and low-volume population	Data source and analysis	Outcomes (Adjusted rates expressed as highest vs. lowest volume, with the lowest volume as the reference group, unless otherwise specified)
	Number of hospitals: 67 **Number of operators:** NR			

Key: ACS – acute coronary syndrome; ALKK – Arbeitsgemeinschaft leitende kardiologische Krankenhausärzte; BCIS – British Cardiovascular Intervention Society; CTO – chronic total occlusion; DES – drug eluting stent; HVH – high-volume hospital; HVO – high-volume operator; IQR – inter-quartile range; J-PCI – Japanese PCI registry; LMPCI – left main percutaneous coronary intervention; LVH – low-volume hospitals; LVO – low-volume operators; MACE – major adverse cardiac events; MI – myocardial infarction; MVPCI – multivessel percutaneous coronary intervention; NCDR - National Cardiovascular Data Registry; NHS – National Health Service; NR – not reported; NSTEMI – non ST elevation myocardial infarction; OR – odds ratio; PCI – percutaneous coronary intervention; STEMI – ST elevation myocardial infarction; UA – unstable angina; VA – Veterans Affairs.
* Level of analysis not included in meta-analysis.
** Covariate used in alternative model(s) to that used in the meta-analysis.
*** Population in this study differs to others studies (explanation in brackets).

Table A.11: Table of characteristics and outcomes for RQ4

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
Randomised controlled trials			
EARLY-MYO Pu (2017)[329] **China**	**Study period:** 01/2014-09/2016 **Total population:** 344 **Number of PI n(%):** 171 (49.7) **Age:** PI: 59 (52–65) PPCI: 58 (50–64) **Male n(%):** PI: 153 (89.4) PPCI: 153 (88.6) **Sponsorship:** Boehringer Ingelheim	**Fibrinolytic agent:** Half-dose alteplase **Adjunctive Therapies:** Aspirin, clopidogrel or ticagrelor. Unfractionated heparin bolus given with alteplase. **No. (%) Killip class I:** PI: 162 (94.7) PPCI: 160 (92.2) **Hypertension n(%):** PI: 91 (53.4) PPCI: 85 (49.7) **Dyslipidaemia n(%):** PI: 33 (19.3) PPCI: 42 (25.6) **Family History of CVD n(%):** PI: 14 (8.1) PPCI: 13 (7.8) **Diabetes mellitus n(%):** PI: 42 (24.8) PPCI: 42 (25.6) **Smoking current/ recent n(%):** NR **Prior MI:** NR **No. of rescue PCI in PI group n(%):** 41 (24)	**30-day all-cause mortality rates n(%):** PI: 1/171 (0.6) PPCI: 2/173 (1.2) **30-day re-infarction rates n(%):** PI: 1/171 (0.6) PPCI: 1/173 (0.6) **30-day heart failure rates n(%):** PI: 23/171 (13.5) PPCI: 28/173 (16.2) **30-day cardiac mortality rates n(%):** PI: 1/171 (0.6) PPCI: 2/173 (1.2) **Cardiogenic shock rates n(%):** NR **30-day total stroke rates n(%):** PI: 0/171 (0) PPCI: 0/173 (0) **30-day ischaemic stroke rates n(%):** PI: 0/171 (0) PPCI: 0/173 (0) **30-day intra-cranial haemorrhage rates n(%):** PI: 0/171 (0) PPCI: 0/173 (0) **30-day total bleeding rates n(%):** PI: 47/171 (27.5) PPCI: 19/173 (11) **30-day major bleeding rates n(%):**

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		No. in PI group received PCI n(%): 161 (94.2) **Median symptom onset to balloon/needle time PI group:** 210 (166–270) **Median symptom onset to balloon/needle time PPCI group:** 280 (214–340) **Median needle-to-balloon time PI group:** 485 **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** NR **Median door-to-balloon time:** NR **Median symptom onset to randomisation time, PI group:** 190 (136–251) **Median symptom onset to randomisation time, PPCI group:** 185 (137–242) **Median randomisation to needle time:** 57 (7–88) **Median randomisation to balloon time:** 110 (50–160)	PI: 1/171 (0.6) PPCI: 0/173 (0) **30-day minor bleeding rates n(%):** PI: 46/171 (26.9) PPCI: 19/173 (11) **Anaphylaxis and other adverse drug events rates n(%):** NR
Vyshlov (2015)[330] **Russia**	**Study period:** NR **Total population:** 326	**Fibrinolytic agent:** Unknown dose tenecteplase or half-dose streptokinase **Adjunctive Therapies:** Clopidogrel, narcotic analgesics, heparin, aspirin and according to indications β-blockers, calcium antagonists, sedatives and antihistamines.	**In-hospital all-cause mortality rates n(%):** PI: 8/164 (4.9) PPCI: 9/162 (5.5) **In-hospital re-infarction rates n(%):** PI: 2/164 (1.2)

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
	Number of PI n(%): 164 (50.3) **Age:** PI: 57.5 ± 10.4 PPCI: 57.9 ± 10.7 **Male n(%):** PI: 115 (70.1) PPCI: 113 (69.8)	**No. (%) Killip class I:** NR **Hypertension n(%):** PI: 139 (84.8) PPCI: 133 (82.1) **Dyslipidaemia n(%):** PI: 142 (86.6) PPCI: 144 (88.9) **Family History of CVD n(%):** NR **Diabetes mellitus n(%):** PI: 34 (20.7) PPCI: 31 (19.1) **Smoking current/ recent n(%):** PI: 108 (66.7) PPCI: 110 (67.9%) **Prior MI:** NR **No. of rescue PCI in PI group n(%):** NR **No. in PI group received PCI n(%):** NR **Median symptom onset to balloon/needle time PI group:** 131.7 ± 88.6 **Median symptom onset to balloon/needle time PPCI group:** 232 ± 71.6 **Median needle-to-balloon time PI group:** NR	PPCI: 0/162 (0) **In-hospital heart failure rates n(%):** PI: 22/163 (13.5) PPCI: 15/162 (9.3) **Cardiogenic shock rates n(%):** NR **Cardiac mortality rates n(%):** NR **Total stroke rates n(%):** NR **In-hospital ischemic stroke rates n(%):** PI: 1/164 (0.6) PPCI: 2/162 (1.2) **Intracranial haemorrhage rates n(%):** NR **Total bleeding rates n(%):** NR **Major bleeding rates n(%):** NR **Minor bleeding rates n(%):** NR **Anaphylaxis and other adverse drug events rates n(%):** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Median first medical contact to needle time: NR **Median first medical contact to balloon time:** 117.02 ± 42.3 **Median door-to-needle time:** NR **Median door-to-balloon time:** 67.8 ± 35.2 **Median symptom onset to randomisation time, PI group:** NR **Median symptom onset to randomisation time, PPCI group:** NR **Median randomisation to needle time:** NR **Median randomisation to balloon time:** NR	
STREAM study (2013)[331-334] **Austria, Belgium, Brazil, Canada, France, Germany, Greece, Italy, Norway, Peru, Poland, Russia,**	**Study period:** 03/2008-07/2012 **Total population:** 1892 **Number of PI n(%):** 944 (49.9) **Age:** PI: 59.7±12.4 PPCI: 59.6±12.5 **Male n(%):** PI: 750 (79.5) PPCI: 740 (78.1) **Sponsorship:**	**Fibrinolytic agent:** Full-dose tenecteplase. Dose was reduced by 50% in patients 75 years or older in 2009. **Adjunctive Therapies:** PI: Low molecular weight enoxaparin, clopidogrel, aspirin, glycoprotein IIb/IIIa antagonists. PPCI: Clopidogrel, aspirin, glycoprotein IIb/IIIa antagonists, heparin, low molecular weight heparin or bivalirudin. **No. (%) Killip class I:** PI: 842/895 (94.1) PPCI: 844/894 (94.4) **Hypertension n(%):**	**30-day all-cause mortality rates n(%):** PI: 43/944 (4.6) PPCI: 42/948 (4.4) **1 year all-cause mortality rates n(%):** PI: 63/944 (6.7) PPCI: 56/948 (5.9) **30-day cardiogenic shock rates n(%):** PI: 41/944 (4.3) PPCI: 56/948 (5.9) **30-day re-infarction rates n(%):** PI: 23/944 (2.4) PPCI: 21/948 (2.2) **30-day heart failure rates n(%):** PI: 57/944 (6)

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
Serbia, Spain, UK.	Boehringer Ingelheim	PI: 434/930 (46.7) PPCI: 414/932 (44.4) **Dyslipidaemia n(%):** NR **Family History of CVD n(%):** NR **Diabetes mellitus n(%):** PI: 113/934 (12.1) PPCI: 123/939 (13.1) **Smoking current/ recent n(%):** NR **Prior MI n(%):** PI:81/940(8.6) PPCI: 98/947 (10.3) **No. of rescue PCI in PI group n(%):** 331/911 (36.3) **No. in PI group received PCI n(%):** 736/915 (80.4) **Median symptom onset to balloon/needle time PI group:** 100 (75–143) **Median symptom onset to balloon/needle time PPCI group:** 178 (135–230) **Median needle-to-balloon time:** 483 **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR	PPCI: 72/948 (7.6) **30-day cardiac mortality rates n(%):** PI: 31/944 (3.3) PPCI: 32/948 (3.4) **1 year cardiac mortality rates n(%):** PI: 38/944 (4) PPCI: 39/948 (4.1) **30-day total stroke rates n(%):** PI: 15/944 (1.6) PPCI: 5/948 (0.5) **30-day intracranial haemorrhage rates n(%):** PI: 9/944 (1) PPCI: 2/948 (0.2) **30-day ischemic stroke rates n(%):** PI: 6/944 (0.6) PPCI: 3/948 (0.3) **Total bleeding rates n(%):** NR **30-day major bleeding rates n(%):** PI: 61/944 (6.5) PPCI: 45/948 (4.8) **30-day minor bleeding rates n(%):** PI: 205/944 (21.7) PPCI: 191/948 (20.2) **30-day anaphylaxis and other adverse drug events rates n(%):** PI: 146/944 (15.5) PPCI: 164/948 (17.3)

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Median door-to-needle time: NR **Median door-to-balloon time:** NR **Median symptom onset to randomisation time, PI group:** 91 (68–132) **Median symptom onset to randomisation time, PPCI group:** 92 (65–132) **Median randomisation to needle time:** 9 (6–13) **Median randomisation to balloon time:** 77 (57–112)	
Bendary (2018)[335] **Egypt**	**Study period:** 12/2016-06/2017 **Total population:** 60 **Number of PI n(%):** 30 (50) **Age:** PI: 52.9 ±10.6 PPCI: 51.7±10.1 **Male n(%):** PI: 21 (70) PPCI: 26 (86.7)	**Fibrinolytic agent:** Full-dose streptokinase **Adjunctive Therapies:** PI: Low molecular weight enoxaparin, clopidogrel, aspirin, beta blockers, ACEIs. PPCI: clopidogrel, aspirin, beta blockers, ACEIs, Unfractionated Heparin. Eptifibatide or Tiroban for thrombus burden. **No. (%) Killip class I:** NR **Hypertension n(%):** PI: 8 (26.7) PPCI: 10 (33.3) **Dyslipidaemia n(%):** PI: 3 (10) PPCI: 4 (13.3) **Family History of CVD n(%):** PI: 3 (10) PPCI: 2 (6.7)	**In-hospital all-cause mortality rates n(%):** PI: 0/30 (0) PPCI: 1/30 (3.3) **30-day all-cause mortality rates n(%):** PI: 1/30 (3.3) PPCI: 1/30 (3.3) **In-hospital re-infarction rates n(%):** PI: 0/30 (0) PPCI: 0/30 (0) **30-day re-infarction rates n(%):** PI: 0/30 (0) PPCI: 1/30 (3.3) **In-hospital heart failure rates n(%):** PI: 4/30 (13.3) PPCI: 3/30 (10) **Cardiac mortality rates n(%):** NR **In-hospital total stroke rates n(%):**

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Diabetes mellitus n(%): PI: 8 (26.7) PPCI: 11 (36.7) **Smoking current/ recent n(%):** PI: 19 (63.3) PPCI: 22 (73.3) **Prior MI n(%):** NR **No. of rescue PCI in PI group n(%):** NR **No. in PI group received PCI n(%):** NR **Median symptom onset to balloon/needle time PI group:** 110 ± 27.5 **Median symptom onset to balloon/needle time PPCI group:** 186.8 ± 16.6 **Median needle-to-balloon time PI group:** 14.2 ± 6.8 (hr) **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** 35 ± 7.9 **Median door-to-balloon time:** 60 ± 10.5 **Median symptom onset to randomisation time, PI group:** NR	PI: 0/30(0) PPCI: 0/30(0) **30-day total stroke rates n(%):** PI: 1/30 (3.3) PPCI: 0/30 (0) **Ischemic stroke rates n(%):** NR **In-hospital major bleeding rates n(%):** PI: 1/30 (3.3) PPCI: 2/30 (6.6) **30-day major bleeding rates n(%):** PI: 3/30 (10) PPCI: 3/30 (10) **Minor bleeding rates:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Median symptom onset to randomisation time, PPCI group: NR **Median randomisation to needle time:** NR **Median randomisation to balloon time:** NR	
GRACIA-4 (2017)[336] **Spain**	**Study period:** 05/2010-01/2014 **Total population:** 355 **Number of PI n(%):** 177 (49.9) **Age:** PI: 62.01 ± 12.98 PPCI: 61.73 ± 12.50 **Male n(%):** PI: 139 (78.5%) PPCI: 149 (83.7%)	**Fibrinolytic agent:** Full-dose tenecteplase **Adjunctive Therapies:** PI: Enoxaparin, aspirin, clopidogrel PPCI: Bivalirudin, clopidogrel, aspirin **No. (%) Killip class I:** PI: 160 (92.0%) PPCI: 161 (93.1%) **Hypertension n(%):** PI: 81 (46.3%) PPCI: 75 (42.1%) **Dyslipidaemia n(%):** PI: 83 (47.4%) PPCI: 70 (39.3%) **Family History of CVD n(%):** NR **Diabetes mellitus n(%):** PI: 28 (16.0%) PPCI: 33 (18.5%) **Smoking current/ recent n(%):** PI: 82 (47.1%) PPCI: 84 (47.2%) **Prior MI n(%):** PI: 14 (8.0%) PPCI: 16 (9.0%)	**30-day all-cause mortality rates n(%):** PI: 4/177 (2.3) PPCI: 4/178 (2.3) **1 year all-cause mortality rates n(%):** PI: 7/177 (4.1) PPCI: 8/178 (4.5) **30-day re-infarction rates n(%):** PI: 2/177 (1.1) PPCI: 5/178 (2.8) **1 year re-infarction rates n(%):** PI: 5/177 (2.8) PPCI: 8/178 (4.5) **Heart failure rates n(%):** NR **30-day cardiac mortality rates n(%):** PI: 4/177 (2.3) PPCI: 4/178 (2.3) **1 year cardiac mortality rates n(%):** PI: 6/177 (3.4) PPCI: 5/178 (2.8) **30-day total stroke rates n(%):** PI: 6/177 (3.4) PPCI: 1/178 (0.6) **1 year total stroke rates n(%):** PI: 8/177 (4.5)

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		No. of rescue PCI in PI group n(%): 71 (40.1) **No. in PI group received PCI n(%):** 158 (90.3) **Median symptom onset to balloon/needle time PI group:** 170 (117.50-240) **Median symptom onset to balloon/needle time PPCI group:** 225 (160-315) **Median needle-to-balloon time PI group:** 430 **Median first medical contact to needle time:** 75 (45-109) **Median first medical contact to balloon time:** 126 (90-175) **Median door-to-needle time:** NR **Median door-to-balloon time:** NR **Median symptom onset to randomisation time, PI group:** 160 (105-221) **Median symptom onset to randomisation time, PPCI group:** 150 (100-225) **Median randomisation to needle time:** NR **Median randomisation to balloon time:** NR	PPCI: 1/178 (0.6) **30-day intracranial haemorrhage rates n(%):** PI: 0/177 (0) PPCI: 0/178 (0) **1 year intracranial haemorrhage rates n(%):** PI: 0/177 (0) PPCI: 0/178 (0) **30-day ischemic stroke rates n(%):** PI: 4/177 (2.3) PPCI: 1/178 (0.6) **1 year ischemic stroke rates n(%):** PI: 6/177 (3.4) PPCI:1/178 (0.6) **30-day total bleeding rates n(%):** PI: 11/177 (6.2) PPCI: 9/178 (5.1) **1 year total bleeding rates n(%):** PI: 14/177 (7.9) PPCI: 13/178 (7.3) **30-day major bleeding rates n(%):** PI: 2/177 (1.1) PPCI: 0/178 (0) **1 year major bleeding rates n(%):** PI: 2/177 (1.1) PPCI: 0/178 (0) **30-day minor bleeding rates n(%):** PI: 9/177 (5.1) PPCI: 9/178 (5.1) **1 year minor bleeding rates n(%):** PI: 12/177 (6.8) PPCI: 13/178 (7.3)

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
Observational studies			
Bessonov (2016)[337] **Russia**	**Study period:** 2008-2013 **Total population:** 721 **Number of PI n(%):** 144 (20) **Age:** PI: 56.9 ± 10.2 PPCI: 59.6 ± 11.2* **Male n(%):** PI: 122 (84.7) PPCI: 419 (72.6)*	**Fibrinolytic agent:** Full-dose tenecteplase **Adjunctive Therapies:** NR **No. (%) Killip class I:** PI: 121 (90.3) PPCI: 484 (90.8) **Hypertension n(%):** PI: 109 (76.2) PPCI: 465 (83) **Dyslipidaemia n(%):** PI: 141 (98.6) PPCI: 538 (96.1) **Family History of CVD n%:** NR **Diabetes mellitus n(%):** PI: 19 (13.3) PPCI: 100 (17.9) **Smoking current/ recent n(%):** NR **Prior MI n(%):** PI: 27 (18.9) PPCI: 93 (16.6) **No. of rescue PCI in PI group n(%):** NR **No. in PI group received PCI n(%):** NR **Median symptom onset to balloon/needle time PI group:** 80 (55-172)	**Adjusted OR (95% CI) of all-cause mortality:** NR **Adjusted OR (95% CI) of total bleeding:** NR **Adjusted OR (95% CI) of major bleeding:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Median symptom onset to balloon/needle time PPCI group: NR **Median needle-to-balloon time:** 270 (120-540) **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** NR **Median door-to-balloon time:** 86 (67-115)	
Siontis (2016)[156] **USA**	**Study period:** 05/2004-12/2012 **Total population:** 1701 **Number of PI n(%):** 364 (21.4) **Age:** PI: 62.7 ± 13.2 PPCI: 64.4 ± 14* **Male n(%):** PI: 275 (75.5) PPCI: 945 (70.7)	**Fibrinolytic agent:** Full-dose Reteplase or Tenecteplase **Adjunctive Therapies:** PI: Aspirin, unfractionated heparin, clopidogrel. PPCI: Aspirin, unfractionated heparin. Eptifibatide at discretion of team. **No. (%) Killip class I:** NR **Hypertension n(%):** PI: 230 (63.2%) PPCI: 838 (62.7%) **Dyslipidaemia n(%):** PI: 227 (62.4%) PPCI: 837 (62.6%) **Family History of CVD n(%):** NR	**Adjusted OR (95% CI) of 30-day all-cause mortality:** 0.66 (0.36-1.21) **Adjusted OR (95% CI) of 5 year all-cause mortality:** 0.84 (0.63-1.12) **Adjusted OR (95% CI) of total bleeding:** NR **Adjusted OR (95% CI) of major bleeding:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Diabetes mellitus n(%): PI: 58 (15.9%) PPCI: 243 (18.2%) **Smoking current/ recent n(%):** PI: 247 (67.9%)* PPCI: 853 (63.8%) **Prior MI n(%):** PI: 68 (18.7%) PPCI: 223 (16.7%) **No. of rescue PCI in PI group n(%):** 153 (42) **No. in PI group received PCI n(%):** 295 (81) **Median symptom onset to balloon/needle time PI group:** NR **Median symptom onset to balloon/needle time PPCI group:** NR **Median needle-to-balloon time:** NR **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** 28 (20-37.5) **Median door-to-balloon time:** ~65	
Victor (2014)[338, 339]	**Study period:** 08/2011-05/2013	**Fibrinolytic agent:** Full-dose Tenecteplase	**Adjusted OR (95% CI) of all-cause mortality:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
India	**Total population:** 200 **Number of PI n(%):** 45 (22.5) **Age:** PI: 54 (46-62) PPCI: 54 (47-61) **Male n(%):** PI: 39 (86.7) PPCI: 134 (86.5) **Sponsorship:** Boehringer Ingelheim provided Tenecteplase	**Adjunctive Therapies:** PI: Aspirin, clopidogrel. Low-molecular weight heparin PPCI: aspirin, lytic and anticoagulants/ antiplatelets at doctor discretion. **No. (%) Killip class I:** PI: 20 (44.4) PPCI: 110 (71%)* **Hypertension n(%):** PI: 14 (31.1) PPCI: 47 (30.3) **Dyslipidaemia n(%):** PI: 5 (11.1) PPCI: 7 (4.5) **Family History of CVD n(%):** PI: 3 (6.7) PPCI: 19 (12.3) **Diabetes mellitus n(%):** PI: 24 (53.3) PPCI: 78 (50.3) **Smoking current/ recent n(%):** PI: 12 (26.7) PPCI: 35 (22.6) **Prior MI n(%):** NR **No. of rescue PCI in PI group n(%):** 4 (12.1) **No. in PI group received PCI n(%):** 33 (73.3) **Median symptom onset to balloon/needle time PI group:**	**Adjusted OR (95% CI) of total bleeding:** NR **Adjusted OR (95% CI) of major bleeding:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		245 (185-395) **Median symptom onset to balloon/needle time PPCI group:** 260 (185-390) **Median needle-to-balloon time:** 12.25 (4.5-23.67) **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** 47 (35-75) **Median door-to-balloon time:** 80 (60-120)	
Sierra-Fragoso (2018)[340] **Mexico**	**Study period:** 01/2016-01/2017 **Total population:** 400 **Number of PI n(%):** 137 (34.2) **Age:** NR **Male n(%):** PI: 106 (77.4) PPCI: 204 (77.6)	**Fibrinolytic agent:** NR **Adjunctive Therapies:** NR **No. (%) Killip class I:** PI: 122 (89.1) PPCI: 236 (89.7) **Hypertension n(%):** PI: 70 (51.1) PPCI: 154 (58.6) **Dyslipidaemia n(%):** PI: 38 (27.7) PPCI: 74 (28.1) **Family History of CVD n(%):** NR **Diabetes mellitus n(%):**	**Adjusted OR (95% CI) of all-cause mortality:** NR **Adjusted OR (95% CI) of total bleeding:** NR **Adjusted OR (95% CI) of in-hospital major bleeding:** 0.42 (0.069-2.5)

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		PI: 66 (48.2) PPCI: 121 (46.0) **Smoking current/ recent n(%):** PI: 82 (59.9) PPCI: 146 (55.5) **Prior MI n(%):** NR **No. of rescue PCI in PI group n(%):** 35 (30.7) **No. in PI group received PCI n(%):** 114 (83.2) **Median symptom onset to balloon/needle time PI group:** NR **Median symptom onset to balloon/needle time PPCI group:** 309 ± 189 **Median needle-to-balloon time:** NR **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** NR **Median door-to-balloon time:** 39 ± 21	

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
Shavadia (2013)[341] **Canada**	**Study period:** 10/2006-03/2011 **Total population:** 3013 **Number of PI n(%):** 1504 (49.9) **Age:** NR **Male n(%):** NR	**Fibrinolytic agent:** Full-dose Tenecteplase **Adjunctive Therapies:** PI: Aspirin, clopidogrel. enoxaparin PPCI: Aspirin, clopidogrel, enoxaparin (prehospital diagnosed), unfractionated heparin (hospital diagnosis). Nitroglycerin and analgesia with morphine as appropriate. **No. (%) Killip class I:** NR **Hypertension n(%):** NR **Dyslipidaemia n(%):** NR **Family History of CVD n(%):** NR **Diabetes mellitus n(%):** NR **Smoking current/ recent n(%):** NR **Prior MI n(%):** NR **No. of rescue PCI in PI group n(%):** 348 (23.1) **No. in PI group received PCI n(%):** NR **Median symptom onset to balloon/needle time PI group:** NR	**Adjusted OR (95% CI) of all-cause mortality:** NR **Adjusted OR (95% CI) of total bleeding:** NR **Adjusted OR (95% CI) of major bleeding:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Median symptom onset to balloon/needle time PPCI group: NR **Median needle-to-balloon time:** NR **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** NR **Median door-to-balloon time:** NR	
Kumbhani (2019)[342] **India**	**Study period:** 2012-2014 **Total population:** 1215 **Number of PI n(%):** 400 (32.9) **Age:** PI: 53.0 ± 10.7 PPCI: 55.0 ± 12.1* **Male n(%):** PI: 348 (87) PPCI: 697 (85.5)	**Fibrinolytic agent:** Unknown dose Streptokinase **Adjunctive Therapies:** Aspirin, clopidogrel **No. (%) Killip class I:** NR **Hypertension n(%):** PI: 79 (19.8) PPCI: 235 (28.8)* **Dyslipidaemia n(%):** NR **Family History of CVD n(%):** NR **Diabetes mellitus n(%):** PI: 86 (21.5) PPCI: 264 (32.4)*	**Adjusted OR (95% CI) of in-hospital all-cause mortality:** 2.05 (0.47-8.93) **Adjusted OR (95% CI) of 1 year all-cause mortality:** 1.12 (0.57-2.21) **Adjusted OR (95% CI) of 2 year all-cause mortality:** 1.12 (0.60-2.1) **Adjusted OR (95% CI) of total bleeding:** NR **Adjusted OR (95% CI) of major bleeding:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Smoking current/ recent n(%): PI: 182 (45.5) PPCI: 259 (31.8)* **Prior MI n(%):** NR **No. of rescue PCI in PI group n(%):** NR **No. in PI group received PCI n(%):** NR **Median symptom onset to balloon/needle time PI group:** NR **Median symptom onset to balloon/needle time PPCI group:** NR **Median needle-to-balloon time:** 18.4 ± 32.3 (hours) **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** 30.0 ± 154.6 **Median door-to-balloon time:** 105.0 ± 178.4	
Rashid (2016)[343] **Canada**	**Study period:** 04/2009-05/2011 **Total population:** 1216 **Number of PI n(%):** 236 (19.4)	**Fibrinolytic agent:** Full-dose Tenecteplase **Adjunctive Therapies:** Aspirin, unfractionated heparin, clopidogrel **No. (%) Killip class I:**	**Adjusted OR (95% CI) of all-cause mortality:** NR **Adjusted OR (95% CI) of total bleeding:** NR **Adjusted OR (95% CI) of in-hospital major bleeding:** 2.02 (0.93-4.41)

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
	Age: PI: 61.2 ± 11.6 PPCI: 62.7 ± 13.3 **Male n(%):** PI: 176 (74.6) PPCI: 710 (72.4)	PI: 220 (93.2) PPCI: 878 (89.7) **Hypertension n(%):** PI: 114 (49.6) PPCI: 462 (47.7) **Dyslipidaemia n(%):** PI: 112 (48.9) PPCI: 405 (42.4) **Family History of CVD n(%):** NR **Diabetes mellitus n(%):** PI: 48 (20.9) PPCI: 159 (16.4) **Smoking current/ recent n(%):** PI: 123 (53.5) PPCI: 396 (40.9)* **Prior MI n(%):** PI: 36 (15.7) PPCI: 132 (13.6) **No. of rescue PCI in PI group n(%):** NR **No. in PI group received PCI n(%):** 201 (85.2) **Median symptom onset to balloon/needle time PI group:** NR **Median symptom onset to balloon/needle time PPCI group:** 204 (141-312) **Median needle-to-balloon time:** 260 (201-385)	

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Median first medical contact to needle time: NR **Median first medical contact to balloon time:** NR **Median door-to-needle time:** 31 (18-60) **Median door-to-balloon time:** NR	
Carrillo (2016)[344] **Spain**	**Study period:** 01/2010-01/2012 **Total population:** 2470 **Number of PI n(%):** 243 (9.8) **Age:** PI: 59.7 (11.8)* PPCI: 62.6 (13.4) **Male n(%):** PI: 204 (83.9) PPCI: 1786 (80.2)	**Fibrinolytic agent:** Unknown dose Tenecteplase **Adjunctive Therapies:** NR **No. (%) Killip class I:** PI: 199 (82.9) PPCI: 1881 (84.8) **Hypertension n(%):** NR **Dyslipidaemia n(%):** NR **Family History of CVD n(%):** NR **Diabetes mellitus n(%):** PI: 40 (16.5%) PPCI: 402 (18%) **Smoking current/ recent n(%):** NR **Prior MI n(%):** PI: 22 (9%) PPCI: 207 (9.3%)	**Adjusted OR (95% CI) of 30-day all-cause mortality:** 1.91 (1.01-3.50) **Adjusted OR (95% CI) of Total bleeding:** NR **Adjusted OR (95% CI) of Major bleeding:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		No. of rescue PCI in PI group n(%): 94 (38.7) **No. in PI group received PCI n(%):** 243 **Median symptom onset to balloon/needle time PI group:** 105 (78–139) **Median symptom onset to balloon/needle time PPCI group:** 172 (136–215) **Median needle-to-balloon time:** NR **Median first medical contact to needle time:** 45 (28–74) **Median first medical contact to balloon time:** 119 (90–153) **Median door-to-needle time:** NR **Median door-to-balloon time:** NR	
Andersson (2019)[345] **USA**	**Study period:** 01/2010-12/2016 **Total population:** 27,205 **Number of PI n(%):** 1,278 (4.7) **Age:** PI: 59.88 ± 11.52 PPCI: 61.66 ± 12.91*	**Fibrinolytic agent:** NR **Adjunctive Therapies:** NR **No. (%) Killip class I:** NR **Hypertension n(%):** PI: 838 (65.6) PPCI: 17,993 (69.4)*	**Adjusted OR (95% CI) of all-cause mortality:** NR **Adjusted OR (95% CI) of in-hospital total bleeding:** 0.83 (0.65-1.07) **Adjusted OR (95% CI) of Major bleeding:** NR

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
	Male n(%): PI: 954 (74.6) PPCI: 18,009 (69.5)* **Sponsorship:** AstraZenecas Efteruddannelseslegat	**Dyslipidaemia n(%):** PI: 773 (60.5) PPCI: 15,892 (61.3) **Family History of CVD n(%):** PI: 202 (15.8) PPCI: 4,361 (16.8) **Diabetes mellitus n(%):** PI: 285 (22.3) PPCI: 6,743 (26.0)* **Smoking current/ recent n(%):** PI: 633 (49.6) PPCI: 11,661 (45.0)* **Prior MI n(%):** PI: 252 (19.7) PPCI: 5,766 (22.2)* **No. of rescue PCI in PI group n(%):** 758 (59.3) **No. in PI group received PCI n(%):** 1,278 (100) **Median symptom onset to balloon/needle time PI group:** 115 (71-200) **Median symptom onset to balloon/needle time PPCI group:** 168 (118-272) **Median needle-to-balloon time:** 223 (137-930) **Median first medical contact to needle time:** NR **Median first medical contact to balloon time:** NR	

First author (year) Country	Population demographics	Therapies, medical history, critical time intervals**	Outcomes
		Median door-to-needle time: NR **Median door-to-balloon time:** NR	

Key: ACM - all cause mortality; ADE - adverse drug reaction ALT – alteplase; CE - composite endpoint; CM - cardiac mortality; CS - cardiogenic shock; CVD – cardiovascular disease; DL – dyslipidaemia; DM – diabetes mellitus; EARLY-MYO - Early Routine Catheterisation After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction; FH – family history; GRACIA-4 - GRupo de Análisis de la Cardiopatía Isquémica Aguda 4; HF - heart failure; HT – hypertension; ICH - intracranial haemorrhage; IQR –interquartile range; IS - ischaemic stroke; MaB - major bleeding; MI – myocardial infarction; MiB - minor bleeding; NBT – needle-to-balloon time; NR – not reported; PI – pharmacoinvasive; PPCI – primary PCI; RBT - require blood transfusion; RET - Reteplase; RH - re-hospitalisation; RI - re-infarction; SD – standard deviation; SOBT – symptom onset-to-balloon time; SONT – symptom onset-to-needle time; STR – Streptokinase; STREAM - Strategic Reperfusion Early after Myocardial Infarction; SU – survival; TB - total bleeding; TEN – Tenecteplase; TIA - transient ischaemic attack.
* - characteristics are statistically significantly different ($p<0.05$) between pharmacoinvasive and primary PCI populations.
** - for critical time intervals, median or mean times can be described, even though 'median' is stated in these columns

Table A.12: Inclusion and exclusion criteria for studies included in RQ4

Author and year	Inclusion criteria	Exclusion criteria
Randomised Controlled trials		
EARLY-MYO (2017)[329]	1. Age: 18 or over and less than 75 years old; 2. Patents with STEMI with symptom onset within 6 h before randomisation; 3. ECG: ≥2 mm ST-segment elevation in 2 contiguous precordial leads or ≥1 mm ST segment elevation in 2 contiguous extremity leads; 4. Patents with an expected PCI-related delay [expected time delay from FMC to first balloon dilation ≥ 90 min, and difference between the time of FMC to balloon dilation minus the time from FMC to start of fibrinolysis ≥60 minutes)] 5. Signed informed consent form prior to trial participation	1. Evidence of cardiac rupture; 2. ECG: new left bundle branch block; 3. "Diagnosis to balloon inflation" time over 3 hours; 4. Fibrinolysis contradictions 5. Severe complication -·Other diseases with life expectancy ≤12 months; any history of severe renal or hepatic dysfunction; neutropenia, thrombocytopenia; known acute pancreatitis; known acute pericarditis and/or subacute bacterial endocarditis; arterial aneurysm, arterial/venous malformation and aorta dissection; 6. Complex heart condition - Cardiogenic shock (SBP <90mmHg after fluid infusion or SBP<100mmHg after vasoactive drugs); PCI within previous 1 month or previous bypass surgery; previously known coronary artery disease not suitable for revascularisation; hospitalisation for cardiac reason within past 48 hours; 7. Not suitable for clinical trial - Inclusion in another clinical trial; ·previous enrolment in this study or treatment with an investigational drug or device under another study protocol in the past 7 days; pregnant or lactating; Body weight <40kg or >125kg; known hypersensitivity to any drug that may be used in the study; inability to follow the protocol and comply with follow-up requirements or other reason that would place the patient at increased risk.
Vyshlov (2015)[330]	The study included patients with STEMI hospital stage in the first 6 hours from the beginning of disease	Cardiogenic shock
STREAM study (2013)[331-334]	1.Age equal or greater than 18 years 2.Onset of symptoms < 3 hours prior to randomisation 3.12-lead ECG indicative of an acute STEMI 4.Informed consent received	1. Expected performance of PCI <60 min from diagnosis or inability to arrive at the catheterisation laboratory within 3 h 2. Previous CABG 3. Left bundle-branch block or ventricular pacing 4. Patients with cardiogenic shock—Killip Class 4 5. Patients with a body weight ≤55 kg (known or estimated) 6. Uncontrolled hypertension, defined as a single BP measurement ≥180/110 mm Hg (SBP ≥180 mm Hg and/or DBP ≥110 mm Hg)

		before randomisation 7. Hospitalisation for cardiac reason within past 48 h 8. Recent administration of any IV or SC anticoagulation within 12 h, or current use of oral anticoagulation 9. Active bleeding or known bleeding disorder/diathesis or the clinical diagnosis known to be associated with increased bleeding risk 10. Any history of central nervous system damage (e.g., neoplasm or spinal surgery) or recent trauma to the head or cranium. 11. Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 m (includes trauma associated current MI) 12. Any known history of haemorrhagic stroke, ischemic stroke, TIA, or stroke of unknown origin 13. Prolonged or traumatic cardiopulmonary resuscitation within the past 2 wk 14. Known acute pericarditis and/or subacute bacterial endocarditis 15. Known acute pancreatitis or known severe hepatic dysfunction. 16. Long-term dialysis or known renal insufficiency 17. Arterial aneurysm and known arterial/venous malformation 18. Pregnancy or lactation or parturition within the previous 30 d; 19. Previous enrolment in this study or treatment with drug or device under another study protocol in the past 7 d 20. Known hypersensitivity to tenecteplase, alteplase, acetylsalicylic acid, clopidogrel, enoxaparin, or any of the excipients or the contrast media used in angiography 21. Inability to follow the protocol and comply with follow-up requirements or any other reason that the patient would be at increased risk if the investigational therapy is initiated
Bendary (2018)[335]	Patients (male/female) aged ≥ 18 years with chest pain lasting > 30 min, ST segment elevation in 2 contiguous leads of at least 1 mm except ≥ 2 mm in V2-3 or presumed new onset left bundle branch block (LBBB). Successful reperfusion after thrombolytic therapy in patients who underwent pharmaco-invasive strategy including: at least 50 % ST segment resolution in the lead with maximum elevation in baseline ECG, improvement of chest pain	Absolute contraindications for thrombolytic therapy, evidence of mechanical complications of MI including cardiogenic shock, noncardiac condition limiting life expectance to less than 6 months, evidence of pre-existing multi-vessel disease not amenable for revascularisation, evidence of pre-existing more than stage 2 chronic kidney disease (CKD) defined as creatinine clearance less than 60 ml/Kg/min, evidence of pre-existing peripheral vascular disease precluding rapid emergent vascular access, and patient refusal to give consent.

GRACIA-4 (2017)[336]	1) Age over 18 years. 2) Diagnosis of STEMI in the first 12 hours from the beginning of the symptoms with the following criteria: a) typical chest pain of more than 30 minutes without response to nitroglycerin and b) elevation of ST segment of at least 1 mm in 2 contiguous leads of the members, at least 2 mm in 2 or more precordial leads contiguous, suspected complete left bundle branch block again appearance or rhythm electrostimulated by pacemakers with typical clinic. 3) Obtained informed consent.	1) Cardiogenic shock 2) Contraindications to the administration of fibrinolytic or bivalirudin: 3) Suspicion or evidence of cardiac rupture. 4) Non-heart disease with a life expectancy of less than 12 months 5) Contraindications to the use of aspirin, ticlopidine, clopidogrel or heparin 6) Known renal impairment (serum creatinine> 221 µmol / L or> 2.5 mg / dL). 7) Multivessel coronary disease identified as not revascularisable 8) Major surgery planned in the next year. 9) Peripheral vascular disease that makes it impossible to perform a cardiac catheterisation 10) History of neutropenia, thrombocytopenia or liver dysfunction. 11) Women of childbearing age, except in case of negative pregnancy test. 12) Inclusion in another clinical trial.
Observational studies		
Bessonov (2016)[337]	NR	NR
Siontis (2016)[156]	Patients diagnosed with STEMI at Mayo Clinic, and patients referred to the institution from regional hospitals.	Patients with suspected initial STEMI diagnosis that was later refuted were excluded from this analysis. Patient refusal. Second or subsequent STEMI event.
Victor (2014)[338, 339]	Adults aged18–75 years with STEMI requiring either primary PCI or fibrinolysis, patients presenting with the onset of symptoms within 12 h, subjects providing informed consent	Patients who were participating in any other study or who were unwilling to comply with the protocol were excluded.
Sierra-Fragoso (2018)[340]	Included patients with STEMI who had emergency PCI.	Patients with cardiogenic shock, incomplete clinical file, and those treated after more than 24 hours from the onset of pain, were excluded from this study.
Shavadia (2013)[341]	Medical charts of all patients with an International Classification of Diseases (9^{th}/10^{th} Revision) code of MI were reviewed to identify all patients with STEMI	NR
Kumbhani (2019)[342]	Consecutive patients with STEMI. Patients 20 years or older with symptoms or signs consistent with an acute coronary syndrome were enrolled after consent was obtained	Those who died before hospital arrival, ECG confirmation, or before informed consent was obtained
Rashid (2016)[343]	Confirmed STEMI patients who had an onset of myocardial ischemic symptoms of <12 h and STsegment elevation of ≥1	STEMI patients who required therapeutic hypothermia

	mm in 2 contiguous leads on a 12-lead electrocardiogram	
Carrillo (2016)[344]	Early STEMI with ≤120 min from symptom onset to FMC (patient delay) assisted by a non-capable PPCI service (either a non-capable PPCI hospital or pre-hospital EMS care).	No reperfusion treatment, incomplete data, FMC undertaken in PCI capable centre
Andersson (2019)[345]	The study population included all patients presenting with STEMI and treated with either primary PCI, rescue PCI, or routine early PCI.	Patients with no valid, mappable Michigan ZIP codes

Key: CABG – coronary artery by-pass graft; CKD – chronic kidney disease; ECG – electrocardiogram; EMS – emergency medical service; FMC –first medical contact; LBBB - left bundle branch block; NR –not reported; PPCI – primary percutaneous coronary intervention; SBP – systolic blood pressure; STEMI – ST-elevation myocardial infarction; TIA – transient ischaemic attack.

Appendix 4 — Recommendations from guidance documents included in RQ2

Key for Tables A.13-A.19 below:
A&E – accident and emergency; ACC(F) – American College of Cardiology (Foundation); ACE – angiotensin converting enzyme inhibitor; ACS – acute coronary syndrome; AHA – American Heart Association; AMA – American Medical Association; API – Association of Physicians of India; ARB – angiotensin II receptor blocker; ASA – acetylsalicylic acid (aspirin); AUC – area under the curve; BCIS – British Cardiovascular Intervention society; BCS – British Cardiovascular Society; CABG – coronary artery bypass graft; CCL – cardiac catheterisation laboratory; CCN – Cardiac Care Network of Ontario; CCS – Canadian Cardiovascular Society; CCU – coronary care unit; CHD – coronary heart disease; CIN – contrast-induced neuropathy; CPAP – continuous positive airway pressure; CQI – continuous quality improvement; CR – cardiac rehabilitation; CSANZ – Cardiac Society of Australia and New Zealand; CTO – chronic total occlusion; DAP – dose-area product; DGK – German Cardiac Society; DML – Dublin Mid Leinster; DNE – Dublin North East; E2B – emergency medical services-to-balloon; EACTS – European Association for Cardio-Thoracic Surgery; ED – emergency department; EMS – emergency medical services; ECG – electrocardiogram; ESC – European Society of Cardiology; FFR – fractional flow reserve; FMC – first medical contact; FTE – full time equivalent; GISE – Italian Group of Hemodynamic Studies; HIPE – hospital in-patient enquiry; IABP – intra-aortic balloon pump; ICCU – intensive coronary care unit; IV – intravenous; IVUS – Intravascular ultrasound; JCS – Japanese circulation Society; LBBB – left bundle branch block; LM – left main; LOS – length of stay; M&M – morbidity and mortality; MACCE – major adverse cardiovascular and cerebrovascular events; NVVC – Netherlands Association of Cardiology; OCT – optical coherence tomography; PCI – percutaneous coronary intervention; PPCI – primary percutaneous coronary intervention; PTCA – Percutaneous transluminal coronary angioplasty; PTCRA – Percutaneous transluminal rotational atherectomy; PTK – Polish Cardiac Society; QA – quality assurance; QI – quality improvement; RCPI – Royal College of Physicians in Ireland; RT – reperfusion therapy; SCAI – the Society for Cardiovascular Angiography and Interventions; SICI – Italian Society of Invasive Cardiology; SO2 – oxygen saturation; SSC – Swiss Society of Cardiology; STEMI – ST-elevation myocardial infarction; SYNTAX – synergy between percutaneous coronary intervention with taxus and cardiac surgery; TIMI – thrombolysis in myocardial infarction; TJC – The Joint Commission; TL – rapid thrombolysis at local hospital.

Table A.13: Recommendations regarding institutional facilities

Organisation (year)	Recommendation(s)
Asia Pacific	
CSANZ (2014b)	**Primary PCI:** ▪ Full support and commitment from hospital administration, fulfilling institutional requirements including support services. ▪ A comprehensive system of care to shorten time between symptom onset and primary PCI should be in place. Ideally this should include an 'in-field activation' programme established in conjunction with local ambulance services to minimize treatment delays. Furthermore a system facilitating early recognition in the Emergency Department with prompt contact with the Cardiology team should be established. Pathways of communication and a clearly defined mechanism of primary PCI activation needs to be implemented prospectively. Real-time data feedback with Emergency Department and catheterisation laboratory staff should be undertaken. ▪ A well-equipped and maintained catheterisation laboratory with high-resolution digital imaging capacity and an appropriately diverse inventory of interventional equipment including intra-aortic balloon pump capability and resuscitative equipment. ▪ Routine primary PCI should only be performed after an elective PCI programme has been established and shown to perform with acceptable morbidity and mortality.

Organisation (year)	Recommendation(s)
	– Institutions should participate in 3-6 month period of implementation, during which time development of a formalized primary PCI programme is instituted that includes establishment of standards, training of staff, logistic development and creation of a quality-assessment and error management system. ▪ A policy of 24/7 primary PCI however should not be offered until in view of the laboratory director, there is sufficient infrastructure (workforce and clinical services) to ensure that procedures can be performed safely outside routine working hours and sufficient appropriately trained interventional cardiologists.
CSANZ (2016)	▪ Facilities providing only elective PCI should have an on-call team available to deal with post-procedural complications for at least 24 hours after the last procedure is performed ▪ There should be access to Coronary Care facilities for routine post procedure management and an Intensive Care Unit to facilitate management of mechanically ventilated patients. All units should have the ability to provide support IABP insertion and subsequent care and also the capability to provide a routine and urgent echocardiographic service. ▪ Individual hospitals should have a written policy covering these issues. It is recommended that these arrangements be reconfirmed at regular intervals (at least yearly) and updated when necessary. **Primary PCI:** ▪ Primary PCI should only be performed after an elective PCI programme has been established and shown to perform with acceptable morbidity and mortality. ▪ A policy of 24/7 primary PCI should not be offered until in the view of the laboratory director, there is sufficient infrastructure (workforce and clinical services) to ensure that procedures can be performed safely outside routine working hours and sufficient appropriately trained interventional cardiologists willing to participate in such a program.
Europe	
ESC/EACTS (2019)	**Non-emergency PCI:** ▪ It should be considered that non-emergency high-risk PCI procedures—such as for LM disease, single remaining patent coronary artery, and complex chronic total occlusions—are only performed by adequately experienced operators at centres that have access to circulatory support and intensive care treatment. **Primary PCI for STEMI:** ▪ It is recommended that the pre-hospital management of STEMI patients should be based on regional networks that are designed to deliver reperfusion therapy effectively in a timely fashion, and to offer primary PCI to as many patients as possible ▪ It is recommended that all EMS, emergency departments, coronary care units, and catheterization laboratories have a written updated STEMI management protocol, preferably shared within geographical networks. ▪ It is recommended that primary PCI-capable centres deliver a 24 h/7 day service and ensure that primary PCI is per formed as fast as possible

Organisation (year)	Recommendation(s)
	▪ It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU, and are transferred directly to the catheterization laboratory
DGK (2015)	▪ The area of the actual cardiac catheter space should be enough space for ventilated patients and possible resuscitation measures (usually not less than 40 m2). ▪ The lighting of the heart catheter room must be regulated. At least one surgical light with sterile cover and sufficient brightness (> 20,000 lux) should be provided. ▪ Mechanical ventilation and oxygen and compressed air supply (suction) are to be installed in the examination room and according to patient access. Ceiling mounted systems on the catheter table are recommended. ▪ The computer of the catheter system should be connected to an uninterruptible power supply (UPS). The cardiac catheterization system should at least be connected to an emergency generator (e.g. diesel). ▪ A space for preparation and post-observation of patients. ▪ The following basic technical and medical equipment should be considered when setting up a cardiac catheterization lab in or near the cardiac catheterization site: – Refrigerator for medicines; – Oximetry device for determining hemodynamic characteristics (e.g., cardiac output and oxygen saturation); – Blood gas analyser, available for emergencies; – Optional devices for determining blood clotting (e.g. ACT, 'activated clotting time'). ▪ The following emergency equipment should be available in a proven place in every cardiac catheter laboratory: – Defibrillator with battery or battery operation; – Pacemaker devices (internal pacing, possibly also for external pacing) with battery or battery operation; – Emergency instruments (intubation set) and emergency medications, suitable for this purpose is a specially designed emergency vehicle (best set up according to the in-house standard). Equipment should be serviced regularly
HSE/RCPI (2012, 2015, 2018)	**Primary PCI:** ▪ Ensure pre-hospital triage with 12 lead ECG application and transmission/interpretation is available via trained and equipped EMS ▪ Recommended important characteristics of designated PPCI centres: – No refusal policy – Adequate CCU/step down beds – Dedicated call service and point/s for ECG reception – relevant skill mix in cath lab - interventional cardiologist, nursing, technical and radiology – Minimum of 2 labs is recommended at 24/7 PPCI centre to ensure access at all times ▪ Facilities to allow access to cardiac rehabilitation and secondary prevention prior to discharge

Organisation (year)	Recommendation(s)
SICI-GISE (2015)	▪ 'Hub & Spoke' model, organized in collaboration with the territorial emergency services and A&E. ▪ Within the Network, a Cardiac Surgery, a Vascular Surgery, a Stroke Unit and a Reference Nephrology for all the various problems related to the interventional management of patients with acute coronary syndrome must be well identified. ▪ Laboratories should have: – One or more hemodynamic-angiographic salt, with sufficient space for the various equipment and for easy movement of the personnel during the examinations and any resuscitation in case of necessity. For each room you need a room of size not less than 32 m 2 in addition to the spaces for the 2 technical compartment (approximately 12 m 2) and the control room (at least 7 m2); – Other premises for the preparation and storage of the material, for washing and dressing of the personnel, for the archiving / image processing and other documentation for each examination; – Adequate space, separated from the cath lab, to be used for decontamination, cleaning, disinfection and sterilization of medical devices. Allow for appropriate and possibly distinct pathways for patients, operators and instrumentation, that guarantee safety; – A system, the so-called 'polygraph', that allows the continuous monitoring and ECG recording (must be visible, although not simultaneously, the 6-lead derived from peripheral electrodes and at least one precordial derivation), the monitoring and simultaneous recording at least two intravascular pressures and / or by means of intracardiac catheters and pressure transducers, and the continuous monitoring of pulse oximetry. Such biological signals must be viewable simultaneously on a monitor (preferably colour) located in the execution of the examination room ('protected' area) that at the central unit, located in the local commands, where they will be printed and possibly stored; – Other specific instrumentation for the measurement of cardiac output, for the determination of the invasive blood oxygen content (emossimetria), and finally for measuring the activated clotting time (ACT); – Drugs and tools for cardiopulmonary resuscitation, comprising temporary pacemaker and defibrillator, laryngoscope for tracheal intubation and cannula, oxygen dispenser, equipment for the percutaneous pericardiocentesis, infusion pumps, suction system, lung ventilator; – IABP (possibly also circulatory assistance systems more complex); – Various tools needed angioplasty and intravascular stent implant, with a complete range of items for types and sizes according to the procedures adopted; – At least one advanced invasive imaging technique (intravascular ultrasound or optical coherence tomography) (essential requirement in laboratories in which it performs the PCI of the common trunk of the left coronary artery); – Pressure guides for the measurement of FFR in dubious cases of stenosis on angiography; – Radiological equipment suitable to ensure high performance in terms of quality, use of the images and safety for the patient and for the operators; – Preparation room and monitoring to ensure the privacy of patients equipped with monitor with the possibility of detection of ECG, oximetry, invasive pressures and non-invasive; – Uninterruptible power supply.

Organisation (year)	Recommendation(s)
	▪ Legal provisions on the prevention of accidents and radiation protection ▪ In the new installation of laboratories it is essential to have an ionization chamber for measuring and recording the dose-area product (DAP). **Primary PCI:** ▪ The laboratory that performs PPCI must be inside a cardiological facility equipped with UTIC where an active cardiological guard is guaranteed 24/24. ▪ The laboratory must be active 24/24 and 7/7 days with interventional cardiologists, resuscitation anaesthetists, nursing staff and medical radiology medical technicians.
NVVC (2016)	▪ At least 2 fully equipped cardiac catheterization laboratories must be present with advanced digital x-ray systems with multiple rotation options and multiple image manipulation systems. Two laboratories are needed to ensure continuity in the event of equipment problems or maintenance work. In addition, this leads to faster access for emergency patients, whereby the cardiac catheterization laboratory must be operational within 30 minutes after the announcement of an acute procedure. ▪ Full facilities for cardiopulmonary support and procedures under general anaesthesia. ▪ Presence of intra-aortic balloon pump. ▪ Intravascular imaging capabilities (IVUS, OCT). ▪ Possibility for intravascular pressure and possibly flow measurements. ▪ Presence of a radiation protection program. ▪ Extensive stock of guiding catheters, balloons, stents, guidewires and special devices. ▪ Additional antithrombotic medication such as GPIIb / IIIa inhibitors or bivalirudin should be present. ▪ Presence of on-call service for 24 hours a day, 7 days a week. **Requirements for new intervention centres:** ▪ Centres with or without on-site surgical backup must comply with all the above requirements within 3 years. ▪ 24-hour service, seven days a week available within 2 years. Until then, out-of-hours and emergency patients are sent to the supervising centre.
PTK (2013)	▪ Equipment requirements: — Start-up phase of invasive cardiology laboratory: ▪ Angiocardiograph with digital image registration; ▪ Apparatuses: automatic syringe, polyphypography (enabling pressure measurements and registration ECG), defibrillator, external cardiac stimulator and a resuscitation kit, a device for counter-pulse intra-aortic (IABP); — Advanced invasive cardiology laboratory: ▪ Angiocardiograph with digital image registration;

Organisation (year)	Recommendation(s)
	▪ Apparatuses: automatic syringe, polyphypography (enabling pressure measurements and registration ECG), defibrillator, external cardiac stimulator and a resuscitation kit, a device for counter-pulse intra-aortic (IABP); — Reference invasive cardiology laboratory: ▪ Angiocardiograph with digital image registration; ▪ Apparatuses: automatic syringe, polyphypography (enabling pressure measurements and registration ECG), defibrillator, external cardiac stimulator and a resuscitation kit, a device for counter-pulse intra-aortic (IABP); ▪ IVUS and FFR cameras; ▪ Provide services 24 hours / day for 'advanced' and 'reference' centres. 'Start-up' centres only need to provide services during office hours; ▪ Room conditions of the interventional radiology lab; ▪ Adequate staff and hospital facilities (including a coronary care unit); ▪ Availability of an anaesthesiologist; ▪ Ventilator availability; ▪ Echocardiography availability; ▪ Start-up or advanced invasive cardiology laboratories must have cooperation with a reference interventional cardiology centre with a department of cardiac surgery to provide continuity of treatment of patients;
SSC (2014)	**Elective PCI:** ▪ On-site intensive or intermediate care unit(s)† **Primary PCI in STEMI or ACS with hemodynamic instability:** ▪ Primary PCI centres must deliver a 24/7 service ▪ On-site intensive care unit. † Definition and minimal requirement for intermediate care unit: — Expertise/availability in: ▪ Advanced cardiac life support (ACLS) ▪ Percutaneous temporary pacemaker ▪ Urgent/emergent Intubation ▪ Continuous ECG monitoring ▪ Continuous noninvasive BP monitoring ▪ Continuous SO2 monitoring ▪ In the absence of an intensive care unit on-site, the know-how and equipment for few-hours mechanical ventilation must be available

Organisation (year)	Recommendation(s)
	▪ For centres without intensive care unit on site, formal collaboration with a tertiary center established for immediate patient transfer in case of intensive care requirement is mandatory.
NHS England (2013)	**Primary PCI:** ▪ Primary PCI centres should operate 24 hours a day, 7 days a week, 365 days a year. ▪ A centre performing primary PCI requires at least two cardiac catheterisation laboratories. ▪ Primary PCI centres should have contingencies (or Business Continuity Plans) to deal with rare occasions when the service has to be temporarily withdrawn (adverse weather, major power failure etc.) ▪ Full resuscitation facilities including a defibrillator, intra-aortic balloon counterpulsation, and an anaesthetic backup must be readily available in any catheterisation laboratory undertaking primary PCI. Biochemistry, haematological, and blood transfusion laboratories should be immediately accessible. ▪ A dedicated multidisciplinary team comprising catheterization laboratory and recovery nurses, radiographers, and technicians will be in place. ▪ Primary PCI centres need appropriate support from other clinical disciplines, particularly anaesthetic and intensive care services.
BCIS and BCS (2015)	▪ Two cardiac catheterisation laboratories (two preferred in case of equipment failure)— one cardiac catheterisation laboratory and a non-cardiac radiological facility used for general radiology backup or a high resolution portable fluoroscopy unit with a small image intensifier is considered the minimum requirement. ▪ Digital Imaging and Communications in Medicine archiving of images — contemporary archiving in a compatible format, stored and accessible for a minimum of 8 years; angiograms stored securely and readily accessible during emergencies. PCI centres remote from surgical centres should have facilities for real-time image transfer. ▪ Physiological assessment facilities in all interventional laboratories — accurate pressure recording, display of the waveforms on multiple simultaneous channels, display and recording of a range of ECG lead configurations, heart rate and oxygen saturation monitoring (for patients who have received sedation and/or analgesia). ▪ Radiation protection mandatory. ▪ Cardiac laboratory equipment – Full resuscitation facilities (including a defibrillator), intra-aortic balloon counter-pulsation, an anaesthetic machine, facilities for monitoring anticoagulation (e.g., activated clotting time) and blood gas analysis, disposable angioplasty equipment (including guide catheters, guide wires, balloons and stents), pericardiocentesis sets and an accessible echocardiography machine. ▪ Additional tools could include intravascular ultrasound (IVUS), optical coherence tomography (OCT), flow and pressure wires and equipment for laser and/or rotational atherectomy.
BCIS (2016)	**Primary PCI:** ▪ All primary PCI centres should provide a STEMI service 24 hours a day, 7 days a week, year-round.

Organisation (year)	Recommendation(s)
	▪ All primary PCI centres should have a minimum of two adjacent cardiac catheterisation laboratories. ▪ Centres should have a specified emergency telephone line for communication with the Ambulance and ECG telemetry facility. Ideally an immediately adjacent dedicated catheter lab entrance should be available for ambulances, which precludes the use of the main Accident and Emergency entrance. – Full resuscitation facilities including a defibrillator, intra-aortic balloon counter-pulsation and an anaesthetic machine should be readily available within the catheterisation laboratories undertaking primary PCI. There should be access to non-invasive positive pressure ventilation (CPAP) and external cardiac massage support (Lucas/Autopulse). Immediate availability of transvenous and external cardiac pacing is essential.
North America	
CCN (2013)	▪ All hospitals that treat STEMI patients should be part of a regional STEMI network, in partnership with a PCI Centre (hub-and-spoke model). – A regional STEMI network should operate 24/7 with a 'no refusal' policy. – The participating PCI Centre should have established relationships with all non-PCI Centres and EMS in its regions. ▪ In addition to the transfer agreements, Referring Hospitals and PCI Centres should establish inter-hospital agreements for the initial acceptance of the STEMI patients and for the repatriation of these patients after treatment. ▪ Rapid transport by EMS, with rapid transfer to a cath lab or a dedicated STEMI assessment bed that is ready to receive the patient, bypassing the receiving PCI Centre's ED, will shorten the time to reperfusion and improve patient outcomes. **Guiding principles for the development of a primary PCI programme (originally listed in a 2010 Report):** ▪ A comprehensive primary PCI programme should include service availability for STEMI or AMI patients 24 hours a day, 7 days a week. – Ensuring the 24/7 availability of primary PCI services does not place extraordinary burden on hospital system resources, including health human resources. ▪ To optimize efficiency, primary PCI services will require a minimum of two cardiac cath labs on-site.
ACCF/SCAI (2012)	▪ The facility must have a robust QA program, clear and documented systems for the urgent transfer of patients to a facility with cardiovascular surgical support, documentation that all medication and indication guidelines are being observed, and 24/7 availability.
ACCF/AHA/SCAI (2013)	▪ The facility must provide the necessary radiological, monitoring, and adjunctive patient support equipment to enable operators to perform in the safest and most effective environment. ▪ The real-time fluoroscopic and acquired image quality must be optimal to facilitate accurate catheter and device placement and facilitate the correct assessment of procedural results. ▪ Physiological monitoring equipment must provide continuous, accurate information about the patient's condition. ▪ Access to other diagnostic modalities such as intravascular ultrasound and fractional flow reserve should be available.

Organisation (year)	Recommendation(s)
	▪ Hemodynamic support devices such as intra-aortic balloon pumps and percutaneous ventricular assist devices should be available in institutions routinely performing high-risk PCI. ▪ These requisite support equipment must be available and in good operating order to respond to emergency situations. ▪ The interventional laboratory must have an extensive support system of specifically trained laboratory personnel. Cardiothoracic surgical, respiratory, and anaesthesia services should be available to respond to emergency situations in order to minimize detrimental outcomes. ▪ The institution should have systems for credentialing, governance, data gathering, and quality assessment. Prospective, unbiased collection of key data elements on all patients and consistent timely feedback of results to providers brings important quality control to the entire interventional programme and is critical to assessing and meeting appropriate use criteria for coronary revascularization.
SCAI/ACC/AHA (2014)	▪ Well-equipped and maintained cardiac catheterization laboratory with high-resolution digital imaging capability. – The capability for real-time transfer of images and hemodynamic data (via T-1 transmission line) as well as audio and video images to review - terminals for consultation at the facility providing surgical backup support is highly recommended. ▪ Appropriate inventory of interventional equipment, including guide catheters, balloons and stents in multiple sizes; thrombectomy and distal protection devices; covered stents; temporary pacemakers; and pericardiocentesis trays. ▪ Access to other diagnostic modalities such as intravascular ultrasound and fractional flow reserve is required. **Primary PCI:** ▪ STEMI receiving centres should be available and on-call 24 hours/7 days a week (no diversion) to perform primary PCI. Primary PCI should not be performed at facilities unless it is provided on a 24/7 schedule.

Table A.14: Recommendations regarding institutional volume

Organisation	Recommendations
Asia Pacific	
CSANZ (2014a)	▪ At least 200 interventions per year with an ideal minimum of 400 interventions per year, including 36 primary PCI cases per year if the centre offers a primary PCI service.
CSANZ (2014b)	**Elective PCI:** ▪ 200+ overall PCI cases per year **Primary PCI:** ▪ 36+ primary PCI procedures for STEMI per year
CSANZ (2016)	**Elective PCI:** ▪ It is not ideal that low volume operators (<100 PCIs per year) perform PCIs in low volume centres (centre performing <400 PCIs per year). **Primary PCI:** ▪ More than 36 STEMIs with primary PCI per year.
API (2011)	▪ Team experience greater than a total of 36 primary PCI per year.
JCS (2013)	▪ Medical institutions must have performed a minimum of 30 cases of open-heart surgery, coronary or aortic bypass surgery annually and a minimum of 200 cases of percutaneous coronary angioplasty annually.
Europe	
ESC/EACTS (2019)	▪ It should be considered that institutions with annual volumes of <400 PCIs collaborate in networks with higher-volume institutions (>400 PCIs per year), with shared written protocols and exchange of operators and support staff. **PCI for acute coronary syndromes:** ▪ Performed at institutions performing ≥400 PCIs per year **PCI for stable coronary artery disease:** ▪ Performed at institutions performing ≥200 PCIs per year
SICI-GISE (2015)	▪ Each centre must perform at least 400 PCI procedures per year. – A lower limit can be considered tolerable when the laboratory is located in geographically remote areas that present considerable difficulties with regard to the rapid transfer of patients or in start-up phase.
NVVC (2016)	▪ There must be made at least 600 therapeutic PCI procedures per year. **Requirements for new intervention centres:**

Organisation	Recommendations
	▪ Before starting to make the centre, it should show or demonstrate that a volume of 400 PCIs per year can be achieved within two years and 600 PCIs per year within three years based on the number of indications for PCI generated in their own centre and other centres of which reference can be expected. ▪ After two years must have passed the minimum of therapeutic 400 PCIs per year. ▪ New intervention centres should start a formal partnership with an existing intervention centre (with both the department of cardiology and cardiothoracic surgery) for supervision, support, backup and training in the initial phase. The supervisory centre must have on-site cardiac surgery and perform at least 800 PCIs of therapeutic per year over the past five years. The supervisory center should continue to perform therapeutic 800 PCIs per year after start-up of the new PCI center.
PTK (2013)	▪ Minimum number of procedures for: – Start-up invasive cardiology laboratory is >240 per year – Advanced invasive cardiology laboratory is >500 per year – Reference invasive cardiology laboratory is >700 per year
SSC (2014)	**Elective PCI:** ▪ Minimum number of procedures for interventional centres: 200 PCI per year. **Primary PCI in STEMI or ACS with hemodynamic instability:** ▪ A minimal number of 300 elective PCI procedures per year for institutions performing PCI in patients with STEMI or ACS with hemodynamic instability.
NHS England (2013)	▪ Primary PCI centres should perform an absolute minimum of 100 primary PCI patients per annum ▪ In practice, most primary PCI centre will treat 300 or more patients per annum
BCIS and BCS (2015)	**Total PCI:** ▪ Minimum centre volume of 400 procedures per annum **Primary PCI:** ▪ Absolute minimum of 100 PPCI procedures per annum. ▪ Centres performing <300 PPCIs/annum should consider annually whether a Network approach which rationalises the number of adjacent PPCI centres would be a more appropriate model of care.
BCIS (2016)	▪ All primary PCI centres should undertake a minimum of 150 primary PCI cases per year unless there is extreme geographical isolation to justify a lower volume service. – If primary PCI centres are consistently performing <150 cases/year, annual review with Commissioners should consider whether local transfer times would support coalescing with adjacent sites and may improve patient outcomes. ▪ Lower volume centres are defined in the guideline as <400 primary PCI procedures per year and higher volume centres as >=400 primary PCI procedures per year.

North America	
CCS (2015)	▪ A PCI centre should perform a minimum annual institutional volume of 400 PCI cases per year.
ACCF/SCAI (2012)	▪ An institution should be considered low volume if <400 PCI procedures are performed each year. ▪ It is recommended that lower-volume institutions (<400 per year) must hold conferences with a more experienced partnering institution, with all staff expected to attend on a regular basis. Weekly cardiac catheterization laboratory conferences should be a mandatory aspect of the quality control and inspection program.
ACCF/AHA/SCAI (2013)	**Elective PCI:** ▪ A minimum institutional volume threshold of 200 PCIs per year. – Institutions performing <200 cases annually must have stringent systems and process protocols with close monitoring of clinical outcomes and additional strategies that promote adequate operator and catheterization laboratory staff experience through collaborative relationships with larger-volume facilities. **Primary PCI:** ▪ Ideally, these procedures should be performed in institutions that perform more than 200 elective PCIs per year and more than 36 primary PCI procedures for STEMI per year.
SCAI/ACC/AHA (2014)	▪ Procedures should be performed in institutions performing >200 total and >36 primary PCI procedures annually.
ACC/AHA/SCAI/AMA (2014)	▪ Given the limitations of the evidence base, the writing committee felt strongly that no specific threshold should be required for these measures, though it did see value in collecting these data for institutional and operator quality assurance.
SCAI (2016)	**Elective PCI:** ▪ Minimum volume of 200 PCIs/year to be achieved by all institutions. **Primary PCI:** ▪ Institutions should perform 36 PPCI/year when possible.

Table A.15: Recommendations regarding operator volume

Organisation	Recommendations
Asia Pacific	
CSANZ (2014a)	**Primary PCI:** ▪ 75 PCIs per year is the recommended minimum including 11 cases per year involving primary PCI for ST elevation myocardial infarction if the operator participates in a routine primary PCI service.
CSANZ (2014b)	**Primary PCI:** ▪ It is recommended that primary PCI for STEMI be performed by appropriately trained higher volume operators experienced in both elective and primary PCI: – 75+ elective PCI procedures per year – 11+ primary PCI cases per year ▪ Primary PCI may be reasonably considered by a high volume operator (experience >1000 PCI cases, including undertaking 11+ primary PCI per year) in an established unit with experience in elective PCI although without a dedicated 24 hours-per-day, 365-days-per-year program.
CSANZ (2016)	**Elective PCI:** ▪ It is not ideal that low volume operators (<100 PCIs per year) perform PCIs in low volume centres (centre performing <400 PCIs per year). ▪ Experienced operators: performed more than 1000 PCI cases. **Primary PCI:** ▪ At least 11 cases per year/operator
API (2011)	▪ >75 primary cases per year
Europe	
ESC/EACTS (2019)	**PCI for acute coronary syndromes or stable coronary artery disease:** ▪ Operators with annual volumes of ≥75 procedures **PCI for left main coronary artery disease:** ▪ Operators with an annual volume of ≥25 LM PCI cases per year
SICI-GISE (2015)	▪ It should be noted that according to the major scientific societies, >75 PCI/operator/year is required for the maintenance of adequate preparation only if the operator works in a laboratory that performs more than 400 PCI/year. ▪ New centres and / or new institution must have a reference interventional cardiologist, with proven management experience/laboratory organization that has performed a number of interventional procedures as first operator above 1000, officially certified.
NVVC (2016)	▪ Perform at least 150 therapeutic PCIs per year as the first operator.

Organisation	Recommendations
	▪ During a 5-year period, an experienced interventional cardiologist (> 1000 PCIs) may temporarily perform less than 150 therapeutic PCIs for 1-2 years, but a minimum of 500 therapeutic PCIs for 5 years is required. ▪ In exceptional cases (long-term illness, pregnancy, study leave), it is possible to deviate from the annual number of procedures / number of hours of continuing training. However, the requirements must be met during 3 out of 5 years. A minimum of 500 therapeutic PCI procedures must be performed in 5 years. **Primary PCI:** ▪ A minimum of 30 primary PCIs on an annual basis in the context of an acute ST elevation myocardial infarction.
PTK (2013)	▪ After training, it is necessary to perform an average of 75 coronary angioplasties per year for the therapeutic treatment (i.e. 225 therapeutic procedures within 3 years)
SSC (2014)	**Elective PCI:** ▪ Minimal annual number of 50 PCI procedures as first operator. **PCI for primary PCI in STEMI or ACS with hemodynamic instability:** ▪ Minimal annual number of 75 PCI cases as first operator.
NHS England (2013)	▪ A minimum of 75 PCI procedures per operator per year is required to maintain competence as an independent operator—that is, one who can decide on PCI as appropriate management, plan the strategy, and perform the PCI.
BCIS and BCS (2015)	▪ 75 PCI procedures per year averaged over 2 years (e.g. 150 cases/2 years) which can include up to a maximum of 30 interventional diagnostic procedures (including a mix of elective and non-elective patients). – Interventional diagnostic procedures include the use of Fractional Flow reserve (FFR), IVUS and OCT (and optical frequency domain imaging) when no PCI ensues. ▪ Operators absent from practice for less than 6 months: no additional training required. ▪ Operators absent for between 6 months and 2 years: a buddy system for 20–50 PCI procedures (proportional to the period of absence). ▪ Operators who have fully trained but have not undertaken any procedures for 2 years or more should perform at least 75 PCI procedures with a mentor. **Primary PCI:** ▪ Operators participating in PPCI cases should undertake an absolute minimum of >50 elective/emergency cases/annum within the emergency PPCI site and a total workload of at least 120 PCI cases plus up to 30 interventional diagnostic procedures.
BCIS (2016)	**Primary PCI:** ▪ All Interventional Cardiologists should undertake a minimum of 20 PPCI procedures per year.
North America	

Organisation	Recommendations
ACCF/SCAI (2012)	▪ The annual minimum operator interventional procedural volume of 75 cases per year has become an accepted standard for ensuring quality. The value of using an annual threshold of 75 cases per year is limited when considering each individual operator. **PCI without onsite surgical cover:** ▪ Current guidelines are endorsed for surgical cover and recommend operators performing PCI without onsite surgery should perform 100 total PCIs per year, including 18 primary PCIs per year and that initial operators at a facility without onsite cardiovascular surgical backup should not begin performing PCI in such facilities until they have a lifetime experience of 500 PCIs as primary operator after completing fellowship.
ACCF/AHA/SCAI (2013)	▪ Interventional cardiologists should perform a minimum of 50 coronary interventional procedures per year (averaged over a 2-year period) to maintain competency. **Primary PCI:** ▪ Primary PCI for STEMI should be performed by experienced operators who perform a minimum of 50 elective PCI procedures per year and, ideally, at least 11 PCI procedures for STEMI per year.
SCAI/ACC/AHA (2014)	▪ Interventional cardiologists should perform a minimum of 50 coronary interventional procedures per year (averaged over a 2-year period) to maintain competency. **Primary PCI:** ▪ At least 11 primary PCI procedures per year.
ACC/AHA/SCAI/AMA (2014)	▪ Given the limitations of the evidence base, the writing committee felt strongly that no specific threshold should be required for these measures, though it did see value in collecting these data for institutional and operator quality assurance.
SCAI (2016)	**Total PCI:** ▪ A minimum PCI volume of 50/year is recommended, averaged over 2 years. **Primary PCI:** ▪ Operators should perform 11 PPCI/year when possible. **PCI without onsite surgical cover:** ▪ Operators should perform at least 50 PCIs/year, including 11 primary PCIs, and the institution should ideally recruit more experienced operators. Less experienced operators should have additional oversight, such as backup support.

Table A.16: Recommendations regarding surgical cover

Organisation	Recommendations
Asia Pacific	
CSANZ (2014b)	**Primary PCI:** ▪ Operator and institutional experience as listed: – Institutional: ▪ 36+ primary PCI procedures for STEMI per year ▪ 200+ overall PCI cases per year – Operator: ▪ 75+ elective PCI procedures per year ▪ 11+ primary PCI cases per year ▪ Proven plan for rapid transport to a cardiac surgical centre ▪ Performed in a timely fashion (< 90 mins) ▪ Case selection must be rigorous – Discretion should be exercised when assessing haemodynamically stable patients with complex infarct related lesions that have TIMI 3 flow. – Urgent transfer to institution with cardiac surgery of patients with high-grade residual left main or multi-vessel disease and clinical or haemodynamic instability after culprit vessel primary PCI, preferably with IABP support.
CSANZ (2016)	▪ For centres without on-site cardiac surgery the laboratory director or his nominee should establish a formal relationship with a cardiac surgical unit. – For rural and regional centres without cardiac surgery ideally the Director should be cross accredited at this referral hospital and perform procedures at this hospital on a regular basis. **Elective PCI:** ▪ Under certain conditions the Cardiac Society believes that appropriately trained individuals can perform coronary interventional procedures safely in hospitals without on-site surgical backup. ▪ All operators and centres should meet the minimum requirements set in the Cardiac Society's 'Guidelines for Competency in Percutaneous Coronary Intervention (PCI)'. ▪ It is not ideal that low volume operators (<100 PCIs per year) perform PCIs in low volume centres (centre performing <400 PCIs per year). ▪ Hospitals should accredit Cardiologists individually to perform PCIs. ▪ Ideally there should be a minimum of 2 appropriately trained interventional cardiologists.

Organisation	Recommendations
	▪ There should be access to Coronary Care facilities for routine post procedure management and an ICU to facilitate management of mechanically ventilated patients. All units should have the ability to provide support IABP insertion and subsequent care and also the capability to provide a routine and urgent echocardiographic service. ▪ Individual hospitals should have a written policy covering these issues. It is recommended that these arrangements be reconfirmed at regular intervals (at least yearly) and updated when necessary. ▪ Facilities contemplating performing coronary interventional procedures without on-site surgical back up should first develop a diagnostic coronary angiography service. – This should operate for 12 months and demonstrate acceptable morbidity and mortality for performance of these procedures before commencing a coronary interventional program. – Consideration may be given to abbreviating this period particularly in circumstances where a highly experienced operator (performed more than 1000 PCI cases) is developing the new interventional service and is supported by appropriately skilled cardiac catheterization staff. ▪ There should be an on call team available for at least 24 hours following the last case to deal with any post-procedural complications. ▪ Rural and regional centres without cardiac surgery should establish a formal liaison with a high volume PCI centre which has on site cardiac surgery. – There should be a formal written agreement with a cardiac surgery team and a policy for the transport of patients to the surgical centre. – There should be a formal agreement to perform high risk elective PCIs at the referral centre.†† – The referral centre should assume joint responsibility for training of medical, nursing and technical staff. – The referral centre should participate in regular case discussion and peer review with the regional centre. ▪ New PCI services, especially those in rural and regional centres more than 1 hour travel time from cardiac surgery, should be initially supervised by an experienced operator (experience of more than 1000 PCI cases), who should be present during cases and mentor less experienced operators. This supervision should continue until the mentor and all operators are satisfied that local policies, facilities, case selection, and outcomes are sufficient to allow the service to operate safely without the presence of the mentor. ▪ Rural and regional centres more than 1 hour travel time from cardiac surgery, should not perform elective, high risk PCIs.†† †† High risk PCIs include: — Patients with: ▪ Left ventricular ejection fraction < 25%. ▪ Unprotected left main stenosis. ▪ Single or multiple target lesions that in aggregate jeopardise over 50% of the remaining viable myocardium. — Target lesion with:

Organisation	Recommendations
	▪ Excessive proximal tortuosity or lesion angulation. ▪ Moderate or greater calcification of the target lesion or proximal segment. ▪ Bifurcation lesions (side branch > 2.25mm) where iatrogenic occlusion of a side branch would be an indication for emergency CABG. ▪ Degenerative vein grafts. ▪ Chronic total occlusion.
JCS (2013)	▪ A minimum of one full-time physician who has provided cardiovascular surgery practice for at least 5 years or at least have a close collaboration with another medical institution who can provide emergency surgical cover when necessary.
Europe	
SICI-GISE (2015)	▪ Elective/emergency PCI can also be undertaken in facilities where there is no cardiac surgery. ▪ Recommended that this activity takes place in centres with large volumes of interventional procedures, where there is a team (minimum 3 hemodynamists) driven by an experienced operator (responsible for the laboratory) that has gained wide, documented and adequate experience with the execution of not less than 1000 PCI procedures as first operator in a tertiary centre. ▪ Formalized protocols with the closest facility offering cardiac surgery are mandatory, aimed at ensuring timely access to the operating room within 90 minutes of the occurrence of the need for surgery.
NVVC (2016)	▪ The presence of on-site cardiac surgery backup is no longer required. – Patients presented for primary PCI sometimes require emergency surgical intervention due to a life-threatening anatomy that is inaccessible to PCI or after suboptimal results from a primary PCI. Because the interval to surgical revascularization takes time, it is important to treat high-risk patients in close contact with the cardio-thoracic surgeon. ▪ Although on-site cardiac surgery backup is not required, immediate contact with a cardio-thoracic surgeon in the backup centre should be possible full time, whereby the imaging should be able to be shared with the surgeon through secure imaging transmission software.
SSC (2014)	**Elective PCI:** ▪ For centres without cardiac surgery on site, a formal collaboration with a tertiary centre is mandatory.
BCIS and BCS (2015)	▪ PCI centres without on-site surgical cover should have a viable protocol for emergency transfer to the nearest surgical centre. – The protocol must be agreed by all stakeholders, including the relevant parties in the non-surgical centre and the surgical centre with which it works, local networks, commissioners, and the ambulance service. – The protocol will need to address the training and availability of staff to accompany the patient, including an anaesthetist when required. – Emergency transfer of patients should occur within a maximum of 1 h, with the ability to start cardiopulmonary bypass within 2 h of the call for surgical intervention. – Necessary equipment should also be considered, including a transportable intra-aortic balloon counter-pulsation pump (IABP).

Organisation	Recommendations
	– BCIS recommends that the feasibility of ambulance transfer of the IABP be tested to confirm it can be achieved within the required 120 min timeline. – A good working relationship with the cardiac surgical team in the surgical centre is essential for all non-surgical PCI centres. – It is considered good practice to undertake a virtual run (without the requirement for actual 'blue light' driving) of a catheter lab to surgical centre transfer with IABP annually.
BCIS (2016)	▪ For those primary PCI sites without on-site cardiac or vascular surgery, written and annually reviewed joint protocols should be in place to allow immediate ambulance transfer if required.
North America	
ACCF/SCAI (2012)	▪ The committee cannot recommend elective PCI programmes without cardiovascular surgical backup that only provide primary PCI coverage during daytime and weekday hours. ▪ All facilities that perform primary PCI in a setting without cardiovascular surgical backup must comply with all current guidelines (such as the SCAI 2007 expert consensus document) on the establishment of such a program, such as: – Clear and documented systems for the urgent transfer of patients to a facility with cardiovascular surgical support. – Operators performing PCI without on-site surgery should perform 100 total PCIs per year, including 18 primary PCIs per year. – Initial operators at a facility without on-site cardiovascular surgical backup should not begin performing PCI in such facilities until they have a lifetime experience of 500 PCIs as primary operator after completing fellowship. ▪ High-risk patients or those with high-risk lesions† should not undergo elective PCI in a facility without on-site surgery. † Patients who may be unsuitable for PCI in a facility without surgical backup: ▪ High-risk patients: – Decompensated congestive heart failure (Killip Class 3 to 4) – Recent (<8 weeks) cerebrovascular accident – Known clotting disorder – Left ventricular ejection fraction ≤30% – Chronic kidney disease (creatinine >2.0 mg/dL or creatinine clearance <60 mL/min) – Serious ongoing ventricular arrhythmias ▪ High-risk lesions: – Left main stenosis ≥50% or 3-vessel disease (>70% proximal or mid lesions) unprotected by prior bypass surgery – Target lesion that jeopardizes an extensive amount of myocardium. Jeopardy scoring systems, such as SYNTAX, may be useful in defining the extent. – Diffuse disease (>20 mm length) – Greater than moderate lesion calcification – Extremely angulated segment or excessive proximal or in-lesion tortuosity – Inability to protect side branches

Organisation	Recommendations
	– Older saphenous vein grafts with friable lesion – Thrombus in vessel or at lesion site – Vessel characteristics that, in the operator's judgment, would impede stent deployment – Chronic total occlusions – Anticipated probable need for rotational or other atherectomy device, cutting balloon, or laser
ACCF/AHA/SCAI (2013)	▪ Primary PCI is reasonable in hospitals without on-site cardiac surgery, provided that appropriate planning for programme development has been accomplished. ▪ Elective PCI might be considered in hospitals without on-site cardiac surgery, provided that appropriate planning for programme development has been accomplished and rigorous clinical and angiographic criteria are used for proper patient selection. ▪ Primary or elective PCI should not be performed in hospitals without on-site cardiac surgery capabilities without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without hemodynamic support capability for transfer. ▪ An institution without on-site surgery with a volume fewer than 200 procedures annually, unless in a region underserved because of geography, should strongly consider whether or not it should continue to offer this service.
SCAI/ACC/AHA (2014)	▪ Written agreements for emergency transfer of patients to a facility with cardiac surgery must exist. ▪ Transport protocols should be tested a minimum of 2 times per year involving both the referring and receiving facility. ▪ Development of agreements with a ground or air ambulance service capable of advanced life support and IABP transfer that guarantees a transport vehicle will be on-site to begin transport in 30 min and arrival at the surgical hospital within 60 min of the decision to declare the need for emergency surgery. ▪ Tertiary facility must agree to accept emergent and non-emergent transfers for additional medical care, cardiac surgery or intervention. ▪ Tertiary centres should be able to establish cardiopulmonary bypass on emergency transfer patients within <120 min of an urgent referral. ▪ Rotational or other atherectomy devices and the treatment of CTOs should not be performed in facilities without on-site surgery.
SCAI (2016)	▪ The institution should ideally recruit more experienced operators. – Less experienced operators should have additional oversight, such as backup support. ▪ Consistent with its design, such facilities should: – Participate in national registries – Routinely utilize risk adjustment tools – Have immediately available consultation with a tertiary care centre – Implement cross training of personnel – Have a well-developed system for expeditious transfer for emergency coronary artery bypass graft (CABG).

Table A.17: Recommendations regarding staffing levels

Organisation	Recommendations
Asia Pacific	
CSANZ (2014b)	**Primary PCI:** ▪ Experienced nursing and technical catheterisation staff with training in interventional laboratories. Personnel must be experienced in managing acutely unwell patients with haemodynamic and electrical instability. – Coronary care unit staff must be adept in haemodynamic monitoring, temporary pacemaker operation and IABP management. ▪ Laboratory staff must be skilled in all aspects of interventional equipment and must participate in an on call schedule permitting laboratory operation 24 hours-per-day, 365-days-per-year. ▪ A policy of 24/7 primary PCI however should not be offered until in view of the laboratory director, there is: – Sufficient infrastructure (workforce and clinical services) to ensure that procedures can be performed safely outside routine working hours. ▪ Appropriately trained interventional cardiologists, willing to participate in such a programme which should ideally include more than 2 interventional cardiologists.
CSANZ (2016)	▪ All cardiac catheter laboratories should have a Director of Laboratory who is experienced in interventional procedures. **Elective PCI:** ▪ Ideally there should be a minimum of two appropriately trained interventional cardiologists. ▪ Facilities providing only elective PCI should have an on-call team available to deal with post-procedural complications for at least 24 hours after the last procedure is performed. **Primary PCI:** ▪ Clearly defined roster of on-call interventionalists - for 24/7 cover, at least 3 Interventional cardiologists are required to maintain an adequate roster but additional Interventionalists may be required depending on case load.
JCS (2013)	**Criteria for Institutions Providing PTCA (PCI; Percutaneous Coronary Angioplasty, Percutaneous Coronary Thrombectomy, and Percutaneous Coronary Stenting):** ▪ Medial institutions must have a minimum of one physician who has provided cardiovascular practice for at least 5 years. **Criteria for Institutions Providing Percutaneous Coronary Angioplasty Using PTCRA (Rotablator):** ▪ Medical institutions must have a minimum of one physician who has provided cardiovascular practice for at least 5 years and a minimum of one full-time physician who has provided cardiovascular surgery practice for at least 5 years.
Europe	
DGK (2015)	▪ Ideally, in addition to the examiner, a sterile assistant at the table is also available if needed, which can be both a doctor and a nursing/medical-technical assistant.

Organisation	Recommendations
	▪ With less staff on call and on weekends, a procedure for further assistance in emergencies should be established.
HSE/RCPI (2012, 2015, 2018)	▪ Relevant skill mix in cath lab - interventional cardiologist, nursing, technical and radiology. ▪ Minimum roster of 1:5 Interventionalist Cardiologists is recommended for 24/7 centres (a minimum of 3 Interventionalist Cardiologists for 9-5 centre)
SICI-GISE (2015)	▪ The necessary staff is composed of at least: – 2 interventional cardiologists in the case of activities of a single room – At least 3 interventional cardiologists if the work is carried out contemporarily in two rooms – There should be a minimum number of 4 interventional cardiologists that operate alternately in the same room in order to ensure the continuity of the activity and to ensure ready availability of shifts 24/24h and 365/365 days year (respecting all contractual rights and being able to cope with unforeseen absences) – 2 nurses per room for routine activities – 1 health medical X-ray room technician – The total number of nurses and medical technicians in medical radiology staff employed at the laboratory should be adequate enough to ensure the ready availability of service (respecting the contractual arrangements existing for such personnel) – A professional figure with coordination functions.
NVVC (2016)	▪ During procedures, at least one interventional cardiologist and two additional members of an intervention team (in any case a nurse and an additional nurse, technician or laboratory technician) must be present at all times. ▪ There are at least 4 interventional cardiologists (at least 3.2 FTE, and at least 0.4 FTE / appointment) associated with and working in the intervention centre to provide full-time service. **Requirements for new intervention centres:** ▪ During its launch, at least two experienced and certified interventional cardiologists serving the centre, after 2 years, at least 3, and after 3 years, at least 4 (FTE 3.2, at least 0.4 Fte / appointment), interventional cardiologists.
SSC (2014)	PCI for primary PCI in STEMI or ACS with hemodynamic instability: ▪ A minimum of 3 experienced PCI operators
BCIS and BCS (2015)	▪ Minimum of two nurses per cath lab and one floater nurse per shift for PCI procedures. In addition, one radiographer and one physiologist per lab. For units with more than one catheter lab, a separate additional coordinator should be considered. ▪ The minimum recommended number of trained interventional cardiologists within a PCI centre is three. Some centres have used joint cover arrangements with neighbouring centres to facilitate the initiation of the service. This arrangement should be regarded as temporary and there is an expectation that a third local permanent colleague will be appointed within 2 years. ▪ A sustainable primary PCI rota for Consultant Cardiologists should comprise a minimum of 6 Interventional Cardiologists and ideally 10.

Organisation	Recommendations
BCIS (2016)	▪ A Catheter lab 'crash team' should include a senior Anaesthetist. This team should have sufficient flexibility in their duties to remain within the catheter lab and allow the revascularisation procedure to be completed. ▪ All Interventional Cardiologists should participate in an agreed 24/7 primary PCI rota ▪ The maximum frequency of on-call rota for any individual should not be more frequent than 1:6 ▪ The minimum staff for a primary PCI case is a Consultant Interventional Cardiologist and at least 4 other individuals, including at least 3 allied health professionals of whom 2 should be able to administer IV drugs.
North America	
ACCF/SCAI (2012)	**Laboratory Director:** ▪ The laboratory director should be a physician with the experience and leadership qualities needed to monitor and control the laboratory environment. ▪ The director's qualifications should include at least 5 years of cardiac catheterization experience and possess recognized skill in the laboratory. ▪ Directors that have not had time to accumulate 500 PCI cases should have a QA system in place, as noted previously, wherein a random number of cases are reviewed by a large-volume PCI center. This should be on a continuing basis until the minimum 500 PCI cases have been satisfactorily achieved and competence established. **General staffing:** ▪ At least 1 technologist, preferably a certified radiological technologist, should be skilled in radiographic and angiographic imaging principles and techniques. ▪ Each laboratory should also be reviewed and managed by a qualified medical physicist in order to provide appropriate teaching, to ensure optimal monitoring equipment is being used and to assist with the actual monitoring of radiation exposure to patients and laboratory personnel. ▪ Equipment related to imaging, diagnosis, and treatment is generally available. This ancillary equipment necessitates at least 1 available technologist within the laboratory to be proficient in the equipment use, maintenance, and general troubleshooting. ▪ A technician with expert computer skills is a very valuable addition to the team to assist with the handling of image transfer methods and archival storage devices, image compression, and to maintain the digital libraries. ▪ On occasion, additional administrative personnel may assist in the optimal functioning of the cardiac catheterization laboratory. Such personnel may include a dedicated case manager, scheduler, inventory manager and related staff, compliance monitor, and database or administrative staff for CQI and QA. ▪ There should be adequate cross-training among laboratory staff so that personnel can rotate responsibilities and provide 24-hour coverage of essential team functions. ▪ During any single procedure, the monitoring technician or nurse must have no responsibility other than monitoring and observing patient status.

Organisation	Recommendations
	▪ It is encouraged that during each procedure at least 1 technologist (and/or physician) should be skilled in radiographic and angiographic imaging techniques. ▪ In complex cases and procedures, the presence of a second physician may be needed for optimal care.
SCAI (2016)	▪ Cardiac catheterisation laboratory team: – Primary operator assisted by a physician trainee and/or physician extenders (e.g. certified technologist, physician assistant, or nurse). – Typically, 1–2 staff are tableside, with an additional 2 staff serving in 'circulating' and 'monitoring/recording' roles. ▪ A nurse providing moderate sedation during the procedure must have no other responsibilities that would compromise continuous patient assessment. In cases where there is concern for using more than moderate sedation, an anaesthesia provider should be present, and policies should be drafted that are consistent with hospital credentialing and state guidelines.

Table A.18: Recommendations regarding time/distance to treatment

Organisation(s)	Recommendations
Asia Pacific	
CSANZ (2014b)	▪ Door-to-balloon times should not exceed 90 minutes. ▪ In non-metropolitan centres with adequate facilities and infrastructure and when the operator felt primary PCI was the preferred treatment strategy, Primary PCI may be reasonably considered by a high volume operator (experience > 1000 PCI cases, including undertaking 11+ primary PCI per year) in an established unit with experience in elective PCI although without a dedicated 24 hours-per-day, 365- days-per-year program.
CSANZ (2016)	**Elective PCI:** ▪ New PCI services, especially those in rural and regional centres more than 1 hour travel time from cardiac surgery, should be initially supervised by an experienced operator (experience of more than 1000 PCI cases), who should be present during cases and mentor less experienced operators. ▪ Rural and regional centres more than 1 hour travel time from cardiac surgery, should not perform elective, high risk PCIs.† † High risk PCIs include: ▪ Patients with: – Left ventricular ejection fraction < 25%. – Unprotected left main stenosis. – Single or multiple target lesions that in aggregate jeopardise over 50% of the remaining viable myocardium.

Organisation(s)	Recommendations
	▪ Target lesion with: – Excessive proximal tortuosity or lesion angulation. – Moderate or greater calcification of the target lesion or proximal segment. – Bifurcation lesions (side branch > 2.25mm) where iatrogenic occlusion of a side branch would be an indication for emergency CABG. – Degenerative vein grafts. – Chronic total occlusion.
API (2011)	▪ Primary PCI (balloon inflation) should be performed within 2 hours after first medical contact in all cases. However, for patients presenting early with a large amount of myocardium at risk, a maximum delay of only 90 minutes after first medical contact seems to be a reasonable recommendation.
Europe	
ESC/EACTS (2019)	▪ Maximum time from first medical contact to ECG and diagnosis <10 min ▪ Maximum expected delay from STEMI diagnosis to primary PCI (wire crossing) to choose primary PCI strategy over fibrinolysis (if this target time cannot be met, consider fibrinolysis) ≤120 min ▪ Maximum time from STEMI diagnosis to wire crossing in patients presenting as primary PCI hospitals <60 mins ▪ Maximum time from STEMI diagnosis to wire crossing in transferred patients <90 min ▪ Maximum time from STEMI diagnosis to bolus or infusion start of fibrinolysis in patients unable to meet primary PCI target times <10 min
HSE/RCPI (2012, 2015, 2018)	▪ The ACS programme recommends that all patients are considered for primary PCI unless transport times to the cath lab are greater than 90 minutes – in these circumstances thrombolysis (pre hospital or in hospital) should be administered. ▪ Timely Reperfusion therapy for STEMI (Heart attack): – First medical contact to balloon ≤120 mins – Door to balloon ≤90 mins – Door to needle ≤30 mins
SICI-GISE (2015)	▪ If time to reach the nearest catheterization laboratory capable of performing primary PCI> 120 min then recommend pharmacological reperfusion strategy with fibrinolysis. ▪ All the medical and paramedical team should be ready for operation within 30 minutes after the activation of the emergency service request. ▪ Formalised protocols with the closest facility offering cardiac surgery are mandatory, aimed at ensuring timely access to the operating room within 90 minutes of the occurrence of the need for surgery.
NVVC (2016)	**Primary PCI:** ▪ Preferably, transport to an intervention centre should be within 30-45 minutes of initial paramedical contact

Organisation(s)	Recommendations
	▪ The cardiac catheterization laboratory should be operational within 30 minutes announcement of an acute process ▪ A 'door-to-needle time' of no more than 30 minutes for patients arriving by ambulance and going directly to the cardiac catheterization laboratory should be sought, and no more than 60 minutes for patients who are primarily assessed in the emergency room. **Requirements for new intervention centres:** ▪ Acceptance of the need for new centres should be motivated from a geographical point of view. ▪ Centres should start a formal partnership with an existing intervention centre. The new centre should not be more than 30-45 minutes away by ambulance. ▪ The cardiac catheterization laboratory should be operational within 30 minutes announcement of an acute process
SSC (2014)	**Primary PCI in STEMI or ACS with hemodynamic instability:** ▪ Must be able to start primary PCI as soon as possible but preferably within 60 minutes from the initial call.
NHS England (2013)	▪ Angioplasty treatment should be performed within 90 minutes of arrival of the patient at the angioplasty site, termed door-to-balloon time, and within 150 minutes of a patient's call for help, termed call-to-balloon time. ▪ Allowing 20-30 minutes for initial assessment of the patient, and a door-to-balloon time of 30-40 minutes for an expected patient, this allows a travel time to the primary PCI centre of 80-100 minutes.
BCIS and BCS (2015)	▪ In view of geographical isolation, this case volume (>300 PPCI patients per annum) may be impractical in some isolated areas but BCIS suggests that for the UK, primary PCI centres should all perform an absolute minimum of 100 PPCI procedures per annum. ▪ Emergency transfer of patients should occur within a maximum of 1 h, with the ability to start cardiopulmonary bypass within 2 h of the call for surgical intervention.
BCIS (2016)	▪ Services should be configured to achieve 'call-to-balloon time' of <150 minutes in ≥75% of patients (excluding cardiogenic shock and out-of-hospital arrest). ▪ Optimal performance of the in-hospital service can be measured by a 'door-to-balloon' time <60 minutes in ≥75% of patients (excluding cardiogenic shock and out-of-hospital arrest).
North America	
CCN (2013)	▪ If the recommended timelines for primary PCI cannot be met, the patient should be given fibrinolysis, with a view to an early invasive strategy post fibrinolysis; – Immediate fibrinolysis therapy (within 30 minutes) should be considered if transfer times are likely to be beyond 90 minutes for EMS to PCI site cases or beyond 120 minutes for non-PCI site to PCI transfer cases for primary PCI. ▪ That all PCI Centres, in collaboration with Regional Base Hospitals, Emergency Medical Services and Referring Hospitals in their catchment area, develop shared and common STEMI protocols to achieve timely access to reperfusion for all patients diagnosed as or suspected of having a STEMI. All Referring Hospitals should have a STEMI protocol with linkages to a PCI Centre.

Organisation(s)	Recommendations
	– The Working Group found that it is important to establish a maximum transport time, which could be different for each region, reflecting the unique circumstances of each. There was general consensus that a maximum drive time of 45 minutes would be appropriate, with some discretion to reflect local circumstances and the patient's condition, in which case the maximum transport time should be established with consideration of staying within the E2B time of 90 minutes.
CCS (2015)	▪ First medical contact to first device time should be less than 90 minutes for patients presenting to PCI centres and less than 120 minutes for those being transferred from the non-PCI centres. ▪ First medical contact to device time to be less than 90 minutes for direct emergency medical services transfers to PCI centres especially for provinces with easy access to cath lab and up to 120 minutes is acceptable for provinces with fewer cath labs. Both times should be reported by all the centres. ▪ The goal should be to meet the target in at least 75% of cases.
ACCF/SCAI (2012)	▪ Systems of care within a community should generally direct STEMI patients to facilities that are able to achieve a door-to-balloon time of 90 minutes.
SCAI/ACC/AHA (2014)	▪ The cardiac catheterization laboratory staff and interventional cardiologist should arrive within 30 minutes of a STEMI activation call. ▪ Facilities should have a plan for triage and treatment of simultaneous presentation of STEMI patients. ▪ For centres without on-site cardiac surgery, a transport vehicle should be available to begin transport within 30 minutes and arrival at the surgical hospital within 60 minutes of the decision of the need for emergency surgery. Surgical intervention should begin within 120 minutes. The performance of elective PCI at facilities that cannot meet these transfer times is discouraged. ▪ The development of PCI facilities within a 30-minute emergency transfer time to an established facility is strongly discouraged.

Table A.19: Recommendations regarding monitoring of standards

Organisations	Recommendations
Asia Pacific	
CSANZ (2014a)	▪ Ongoing audit of centre/operators procedural outcome and complications. ▪ Regular case and angiogram image review by the cardiologists and others as appropriate. ▪ Regular mortality / morbidity review by the cardiologists and others as appropriate.
CSANZ (2014b)	▪ On-site rigorous data collection, ongoing programme of outcomes review, benchmarking, quality improvement and formalized periodic case analysis.

Organisations	Recommendations
	▪ Door-to-balloon times should be frequently reviewed as a component of quality assessment with a view to implementing strategies permitting optimal reperfusion within 90 minutes of presentation. ▪ Careful and complete record keeping and peer-review auditing of individual and procedural results is mandatory and an intrinsic part of quality assurance related to primary PCI procedures (whether undertaken with or without surgical backup).
CSANZ (2016)	▪ Careful and complete record keeping and peer-review auditing of individual and procedural results is mandatory and an intrinsic part of quality assurance related to coronary angiography and coronary interventional procedures.
Europe	
ESC/EACTS (2019)	**Quality Indicators:** ▪ Pre-interventional – Adherence to guideline-recommended pre-treatment ▪ Interventional technique – Procedural success – Percentage of radial arterial access – Percentage of drug-eluting stent implantation ▪ Peri-interventional outcome rates – Death – Periprocedural myocardial infarction – Stroke – Contrast-induced nephropathy – Major bleeding (Bleeding Academic Research Consortium 3 - 5) – Emergency coronary artery bypass surgery ▪ Discharge – Antiplatelet medication prescription – High-dose lipid lowering treatment prescription – Adherence to guideline-recommended discharge medications depending on clinical setting ▪ Follow-up – Readmission rates – 30 day and 1 year mortality – Unplanned repeat revascularization at 1 year – Stent thrombosis according to Academic Research Consortium criteria – Major bleeding (Bleeding Academic Research Consortium 3 - 5) – Composite of all-cause death, any myocardial infarction, and any unplanned repeat revascularization at 1 year
HSE/RCPI (2012, 2015, 2018)	**Key performance indicators (KPIs):**

Organisations	Recommendations
	▪ Type of Reperfusion therapy for STEMI (Heart attack) – Description: The % STEMI patients (or LBBB) who get PPCI or thrombolysis reperfusion therapy (RT) or are contraindicated – Rationale: International evidence supports PPCI at a Cath lab centre with good throughput if achievable within the travel time of 120 mins. Current treatment is mainly rapid thrombolysis at local hospital (TL). – Target: 80% of STEMIs in Ireland to get PPCI as form of RT ▪ Timely Reperfusion therapy for STEMI (Heart attack) – Description: The % STEMI patients (or LBBB) who get timely reperfusion therapy ▪ First medical contact (FMC) to balloon ≤120 mins OR ▪ Door to balloon ≤90 mins OR ▪ Door to needle ≤30 mins – Rationale: International evidence supports swift restoration of blood flow to blocked coronary artery as a medical emergency. Current treatment is mainly rapid thrombolysis at local hospital (TL) but newest form of treatment is emergency primary angioplasty (PPCI) at Centre. – Target: 90% achieve timely RT (as defined previously) ▪ Length of stay in hospital – Description: The median LOS for: ▪ STEMI patients ▪ NSTEMI patients – Rationale: ▪ For STEMI the change in treatment from thrombolysis to primary angioplasty will result in a reduction in LOS of ~1 day when the programme is fully up and running. ▪ For NSTEMI early angiography is now indicated to inform treatment. It has the added advantage of improving LOS considerably. Initial goal is reduction of 1 day but is likely to be greater once the programme is fully operational. – Target: ▪ Median LOS for STEMI 2009 HIPE data IRELAND = 5, DML = 4, DNE = 5, South = 4, West=5. Target Ireland and all regions with LOS= 4. ▪ Median LOS for NSTEMI 2009 HIPE data IRELAND = 6, DML = 5, DNE = 7, South = 5, West = 6.5 Target Ireland and all regions with LOS=5. ▪ Early referral for cardiac rehabilitation – Description: The % of ACS patients, admitted as an emergency, who are referred to an early Cardiac rehabilitation programme/secondary prevention programme on discharge (First appointment within 4 weeks of discharge) – Rationale: There is robust evidence indicating that exercise based CR programmes improve risk factors among patients with CHD leading to a reduction in total mortality (20-30%) and cardiac mortality (30%) – Target: 90% of eligible patients by 2013

Organisations	Recommendations
	▪ Discharge bundle – Description: The percentage of eligible (not contraindicated) ACS patients who receive these elements of care on discharge - Medication (ASA, B Blockers, Statin and ACE/ARBs) and smoking cessation counselling – Rationale: The evidence for a secondary prevention programme of medication and smoking cessation advice in reducing morbidity and mortality is extensive – Target: 90% of all eligible patients
SICI-GISE (2015)	▪ Monitoring of some parameters is necessary for both internal and external evaluation of the quality level of the laboratory; these parameters must be made available for comparative assessments at regional and national level, for adherence to registers and for the evaluation of the effectiveness and economic sustainability of new technologies and acceptance of the quality program. The internal audit tool seems to be the easiest way to achieve the purpose, even if it is plagued by numerous limitations. The creation of regional registers in collaboration with the respective Health Departments could be a more effective solution and able to compare different realities within the same geographical area. It is desirable that laboratories be provided with a database which, in addition to information on procedures (clinical indications, injuries) treated, materials used, etc.), report on in-hospital and medium-long term outcome data.
NVVC (2016)	▪ All procedures must be recorded in a database, which must in any case contain the following information: indication of the procedure, technique and materials used, fluoroscopy time, duration of the procedure (from puncturing to removal of the guiding catheter), result of the procedure, complications, coronary artery bypass surgery and mortality. Preferably there is also information about hospital discharge. ▪ Participation in a national registration system for PCI as used by the NVVC.
PTK (2013)	▪ Monthly reporting to a nationwide database
SSC (2014)	▪ Setup of a local database and participation of all centres in the nationwide yearly data collection on interventional procedures and in-hospital mortality with publication of the data on the website of the working group separately for each centre. ▪ Mandatory assessment and reporting of: – Rates of revascularization procedures (PCI and CABG) following diagnostic coronary angiography. – Ratio of the number of overall PCI performed to the number of overall patients treated. – Standardized PCI related inhospital mortality data, STElevation myocardial infarction (STEMI) related mortality, procedure related versus nonprocedure related mortality and mortality in patients after or during cardiopulmonary resuscitation). ▪ Participation of all centres performing primary PCI in the Swiss infarction registry. ▪ Auditing of the facilities by the Working group in agreement with the SSC according to the present recommendations: – Mandatory for each new interventional centre within the first 6 months of activity. – Further auditing only by necessity/on special request.
NHS England (2013)	▪ All primary PCI centres should submit their procedural and outcome data on-line to the BCIS database. The data will then be analysed to give primary PCI centres information on their processes (Call-to-balloon time, door-to-balloon time etc.), their

Organisations	Recommendations
	outcomes (mortality etc.) and whether any patient groups are under-represented in their treated population (e.g. patients over the age of 80). – This procedural and outcome data will be provided by named centre, for all centres performing primary PCI. ▪ Things to be audited: – The percentage of patients achieving a Call-to-balloon time of 150 minutes or less and will be 75% or greater. – The percent of direct referrals from the ambulance service. – Door-to-balloon times. These will vary depending on the route of admission will be less than 45 minutes for daytime presenters and for those patients about whom there has been advance warning (direct ambulance referrals and inter-hospital transfers).
BCIS and BCS (2015)	▪ All PCI centres are expected to collect comprehensive and accurate data that relate to the interventional treatment they provide for their patients. This includes information pertaining to the structure of service provision, the appropriateness of intervention, and the process and outcomes of PCI. ▪ Regular departmental discussions should include individual case presentations for all unexpected mortality and morbidity. ▪ BCIS will provide operators with a detailed breakdown of their own PCI activity that includes risk-adjusted outcome analysis. ▪ BCIS provides a clinical data set to allow a national comparison of results of interventional techniques and comparative audit. ▪ Each cardiology department should provide the name of a designated clinician to lead the audit process and ensure that the infrastructure is in place.
BCIS (2016)	▪ Optimal performance of the in-hospital service can be measured by a 'door-to-balloon' time <60 minutes in ≥75% of patients (excluding cardiogenic shock and out-of-hospital arrest). ▪ If primary PCI centres are consistently performing <150 cases/year, annual review with Commissioners should consider whether local transfer times would support coalescing with adjacent sites and may improve patient outcomes.
North America	
CCN (2013)	▪ As part of an ongoing quality monitoring program, drive times and the rate of complications should be monitored to determine whether there is a relationship between these variables. ▪ PCI Centres should continue to monitor arrival to cath lab to balloon inflation times to ensure that they are within the recommended guidelines. ▪ There is a need for a provincial quality assurance programme to: – Facilitate transparency and benchmarking of different models for STEMI programs. – Support new STEMI networks. – Create standardized definitions for performance indicators. – Monitor performance and provide recommendations including, but not limited to, procedural success, patient outcomes and major adverse cardiovascular events. – Promote coordinated care between EMS, Referring Hospitals and PCI Centres.

Organisations	Recommendations
	Recommended System Measures and Target Times ▪ Proportion of true STEMI patients receiving reperfusion with either primary PCI or fibrinolysis ▪ Ratio of STEMI patients receiving primary PCI versus fibrinolysis ▪ Proportion of fibrinolysis STEMI patients who are cathed within 24 hours of fibrinolysis ▪ Proportion of inappropriate cath lab activations ▪ Time to fibrinolysis therapy: – Door-to-needle time ▪ For in-hospital lysis: ED arrival to administration of lytic: 30 minutes ▪ For pre-hospital lysis: Scene arrival to administration of lytic 30 minutes ▪ Time to primary PCI – Door-to-balloon time ▪ For walk-in patients arriving at PCI Centre: 90 minutes ▪ For patients arriving at Referring Hospital: 120 minutes – EMS arrival at patient to balloon time ▪ For EMS with field ECG to cath lab: 90 minutes ▪ Time to first ECG – 10 minutes ▪ Time from arrival at ED to departure from ED – ED arrival to EMS transfer: 30 minutes
CCS (2015)	▪ Annual reporting of PCI volume: – By centre and provider. – Sequential trend analysis by year. – Can also be reported as a median at a hospital (operators only), regional, provincial, or national level. ▪ First medical contact to first device time for primary PCI: – Reporting by region, and institution, with sequential trend analysis. – Results will be reported as a median or the 25th and 75th percentiles for the selected population and observation period.
ACCF/SCAI (2012)	▪ A continuous QA/QI programme must be considered an essential component of the cardiac catheterization laboratory. It should be dedicated to the lab but not be independent of the other hospital programs. ▪ All cardiac catheterization laboratories should participate in a national or regional registry to benchmark their results and provide an ongoing system for tracking complications. ▪ All major complications in any laboratory should be reviewed by the QA committee at least every 6 months, and individual operator complication rates exceeding national benchmarks for 2 contiguous 6-month periods should be reviewed by the QA director.

Organisations	Recommendations
	▪ Any institution that falls >2 standard deviations outside the risk-adjusted national benchmarks in mortality or emergency same-stay CABG during 2 of 3 contiguous 6-month periods have an external audit looking for opportunities to improve quality of care. **Outcomes-Related Indicators:** ▪ Physical outcomes – Individual physician MACCE – Death – Stroke/nerve injury – MI – Respiratory arrest – Perforation of vessel of heart with sequelae – Nerve injury – Radiation injuries – Emergent cardiovascular surgery – Access site complications – Access site complications requiring surgery – Rate-based outcomes (outcomes related to volume) – Diagnostic cardiac catheterization completion rates – PCI success rates – Normal cardiac catheterization rates ▪ Service outcomes – Access to facility information – Door-to-balloon times – Satisfaction surveys ▪ Financial outcomes – Procedural costs (as laboratory and as individual physician) – Risk management/litigation costs
ACCF/AHA/SCAI (2013)	▪ Each institution that provides PCI services must establish an ongoing mechanism for valid and continuous peer review of its quality and outcomes. ▪ To reach these goals, every PCI programme should operate a quality improvement programme that routinely: – Reviews quality and outcomes of the entire program; – Reviews results of individual operators; ▪ Low volume operators (<50 PCIs annually) should undergo a more intensive review process ▪ Comparison of individual and aggregate outcomes against national standards and benchmark databases

Organisations	Recommendations
	– Includes risk adjustment; ▪ Requires that the institution maintain meticulous and confidential records that include patients' demographics and clinical characteristics – Provides peer review of difficult or complicated cases; and – Performs random case reviews. ▪ An independent and dedicated committee should be established and ideally include both physicians and relevant healthcare personnel in a cooperative effort minimizing any conflicts of interest. Interventional cardiologists are best suited to perform the primary role in evaluating PCI quality and leading the quality assurance program. ▪ The process should be instituted with the support of hospital administrators, who can help provide resources for registry participation, conduct analyses, and support other aspects of the QI process. ▪ Confidential and constructive feedback of performance and outcomes data should be given to clinicians to promote changes in practice and improve performance. ▪ The review process should assess the appropriateness of the interventional procedures. Evaluation should include both the clinical criteria for the procedure and the quality and interpretation of the angiograms.
SCAI/ACC/AHA (2014)	▪ Satisfactory outcomes should be defined by each local facility as part of their quality review process and should be based on national or regional benchmarks. ▪ Programmes that fail to meet their established criteria for satisfactory performance for 2 consecutive quarters must undertake efforts to improve, engaging outside experts if necessary. Failure to improve quality metrics should also be grounds for programme closure regardless of the location. ▪ To ensure proper assessment and monitoring, laboratories are required to submit data to a national data registry, have regular meetings to discuss key performance metrics and develop plans for the correction of any deficiencies. – Monthly multidisciplinary team meetings to evaluate outcomes and quality improvement data. – Operational issues should be reviewed, problems identified, and solutions implemented. ▪ The following measurements should be evaluated on an ongoing basis: – Door-to-first device time, non-transfer patients – STEMI Referral Hospital ED door-to-balloon (first device used) time – First medical contact to balloon inflation (first device used) time, non-transfer patients – First medical contact to balloon inflation (first device used) time, transfer patients – Proportion of eligible patients receiving reperfusion therapy – Proportion of eligible patients administered guideline-based class I therapies – Proportion of patients with field diagnosis of STEMI and activation of the Cardiac Catheterization Laboratory for intended primary PCI who ▪ Do not undergo acute catheterization because of misdiagnosis

Organisations	Recommendations
	▪ Undergo acute catheterization and found to have no elevation in cardiac biomarkers and no revascularization in the first 24h – In-hospital mortality
ACC/AHA/SCAI/AMA (2014)	▪ Every catheterization laboratory should participate in a national or regional PCI registry for benchmarking purposes.
SCAI (2016)	▪ Every CCL must have a quality assurance (QA) program, which includes appropriate quality registries, and at least quarterly, scheduled QA/case review and/or M&M conferences. ▪ Quality registries may be regional or national and should allow for anonymous benchmarking of process and outcome metrics against other operators and institutions. ▪ Each CCL should have a Quality Committee that includes the director, manager, and representatives of other stakeholders. This committee is responsible for reviewing complications not discussed in M&M conferences and other metrics of CCL quality, such as completion of time-outs, quality assurance checks of equipment, door-to-balloon times, and others as required by the hospital, state department of health, and TJC. ▪ Hospitals should provide dedicated, trained personnel to perform chart abstraction, data entry, registry query, and report generation/distribution. ▪ Registries should be utilized to monitor operator and institutional volumes and outcomes as well as procedural appropriateness. ▪ It is important that when comparing outcomes (e.g., bleeding, CIN, mortality) across operators/institutions that these rates be risk-adjusted. ▪ Diagnostic and interventional cases should be randomly selected and peer reviewed for all operators. Ideally, peer review should be blinded and, when possible, performed by physicians external to the hospital/program. Cases should be reviewed for their appropriateness and for any complications. However, AUC ratings should not be used to judge all cases since there are times when patient preference or clinical judgment calls for a procedure. In such circumstances, clear documentation is necessary. While the current AUC criteria are a useful framework, not all indications have been rated and there is still much to be learned about how they impact quality of care and outcomes.

Appendix 5 — Guidance documents with recommendations on time-to-treatment only or for specific conditions/procedures or new PCI centres (RQ2)

Table A.20: Guidance documents making recommendations about time-to-treatment only

Organisation(s), Country/region (year)	Title	Recommendation(s)
International		
ILCOR, International (2015)	2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations – Part 5: Acute coronary syndromes	▪ In patients with STEMI presenting less than 2 h after symptom onset, when primary PCI will result in a delay of greater than 60 min, we suggest fibrinolysis in comparison with PPCI (weak recommendation, low-quality evidence). ▪ In patients with STEMI presenting 2–3 h after symptom onset, when PPCI will result in a delay of 60–120 min, we suggest either fibrinolysis or PPCI (weak recommendation, low-quality evidence). ▪ In patients with STEMI presenting 3–12 h after symptom onset, when PPCI will result in a delay of up to 120 min, we suggest PPCI in comparison with fibrinolysis (weak recommendation, very-low quality evidence).
Asia-Pacific		
CSANZ (New Zealand Branch), New Zealand (2012)	New Zealand 2012 guidelines for the management of non ST-elevation acute coronary syndromes	▪ A 12-lead ECG should be obtained within 10 minutes of patient presentation. ▪ Patients at very high risk should go to the cath lab emergently ≤2 hours if they have refractory angina, with associated heart failure, life threatening ventricular arrhythmias, hemodynamic instability or recurrent marked (≥1 mm) dynamic ECG changes or ≥1 mm ST depression V2–V4 (electrodes used to detect the electrical activity of the heart during an ECG) indicative of circumflex occlusion. – Immediate arrangement must be made for immediate transfer from a non-PCI hospital to a PCI capable Hospital. – Advanced age, frailty, co-morbidities, procedural risk, ability to benefit, and patient preferences must be taken into account.
CSANZ (New Zealand Branch), New Zealand (2013)	ST-elevation myocardial infarction: New Zealand management guidelines, 2013	▪ Patients presenting at locations requiring transport times to the nearest hospital of greater than 45 minutes and FMC to device time >120 minutes, should be considered for administration of pre-hospital fibrinolysis. ▪ Time targets for primary PCI: – FMC to ECG <10 minutes

Organisation(s), Country/region (year)	Title	Recommendation(s)
		– Door-to-device <90 minutes – Transfer-to-device <120 minutes
ACSQHC, Australia (2014)	Acute Coronary Syndromes Clinical Care Standard	▪ A patient with acute chest pain or other symptoms suggestive of an acute coronary syndrome receives a 12-lead ECG and the results are analysed by a clinician experienced in interpreting an ECG within 10 minutes of the first emergency clinical contact. ▪ In general, primary PCI is recommended if the time from first medical contact to balloon inflation is anticipated to be less than 90 minutes, otherwise the patient is offered fibrinolysis.
ANZCOR, Australia and New Zealand (2016)	ANZCOR Guideline 14.3 – Acute Coronary Syndromes: Reperfusion Strategy	▪ The maximum acceptable delay from presentation to balloon inflation is: – 60 minutes if a patient presents within 1 hour of symptom onset; or – 90 minutes if a patient presents later ▪ It is reasonable to consider direct transport to PCI capable facilities for PPCI for patients diagnosed with STEMI by emergency medical services in the prehospital setting, bypassing closer hospitals as necessary, in systems where time intervals between first medical contact and balloon time are brief (<2 hours). ▪ When long delays to PPCI are anticipated (more than 120 minutes), a strategy of immediate fibrinolysis followed by routine early (within 3–24 hours) angiography and PCI, if indicated, is reasonable.
NHFA/CSANZ, Australia and New Zealand (2016)	National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016	▪ It is recommended that a patient with acute chest pain or other symptoms suggestive of an ACS receives a 12-lead ECG and this ECG is assessed for signs of myocardial ischaemia by an ECG-experienced clinician within 10 minutes of first acute clinical contact. ▪ Primary PCI is preferred for reperfusion therapy in patients with STEMI if it can be performed within 90 minutes of first medical contact; otherwise fibrinolytic therapy is preferred for those without contra-indications. ▪ Clinical Circumstances where the Administration of Fibrinolytic Therapy (Assuming 'Door-to-Needle' Time ≤30 Minutes) Should be Considered the Default Reperfusion Strategy: – Patients presenting to ED or suitably trained pre-hospital paramedic teams within 60 minutes of symptom onset. – Patients presenting within 60-120 minutes after symptom onset in whom the expected delay to first device time is >90 minutes. – Unacceptable delays in cardiac catheter laboratory activation for primary PCI. – Patient factors likely to impede successful performance of primary PCI: e.g. severe contrast allergy or poor vascular access.

Organisation(s), Country/region (year)	Title	Recommendation(s)
API, India (2014)	2013 consensus statement for early reperfusion and pharmaco-invasive approach in patients presenting with chest pain diagnosed as STEMI (ST elevation myocardial infarction) in an Indian setting	▪ Medical contact at the level of Primary PCI capable hospital/Center: – If the Door to Balloon time is expected to be < 90 minutes, then Primary PCI is recommended ▪ First/Second Medical Contact at the level of Emergency physician at Non-PCI capable hospital/ nursing home capable of fibrinolysis: – Transfer to primary PCI capable center only if 'transfer time' (first medical contact to PCI capable hospital) is < 30 minutes
CSI, India (2017)	Cardiological Society of India: Position statement for the management of ST elevation myocardial infarction in India	▪ Primary PCI performed by an experienced team within 120 min of FMC (preferably within 90 min)
Emcure Pharmaceuticals Ltd., India (2018)	Expert Consensus Document on Management of ST-Elevation Myocardial Infarction: Adaptation of 2012 ESC Guidelines	▪ Preferred for FMC to ECG and diagnosis: ≤10 min ▪ Preferred for FMC to fibrinolysis ('FMC to needle'): ≤30 min ▪ Preferred for FMC to primary PCI ('door to balloon') in primary PCI hospitals: ≤60 minutes ▪ Preferred for FMC to primary PCI: ≤90 min (≤60 min if early presenter with a large area at risk) ▪ Acceptable for primary PCI rather than fibrinolysis: ≤120 min (≤90 min if early presenter with a large area at risk) if this target cannot be met, consider fibrinolysis
MOH/NHAM/AMM, Malaysia (2009)	Clinical practice guidelines - Management of percutaneous coronary intervention (PCI)	▪ PCI time delay ((door-to-balloon time) minus (door-to-needle time)) is less than 60 minutes ▪ The door to balloon time should be within 90 min if the patient presents at a PCI capable facility ▪ If transferred from a center with no PCI facilities, it should be less than 2 hours (including transfer delay)
MOH/NHAM/AMM, Malaysia (2014)	Clinical practice guidelines - Management of acute ST segment elevation myocardial infarction (STEMI)	▪ The goals of time to reperfusion therapy should be within: ▪ 30 minutes DNT ▪ 90 minutes DBT ▪ 60 minutes PCI time delay ((door-to-balloon time) minus (door-to-needle time))
TSOC, Taiwan (2012)	2012 Guidelines of the Taiwan Society of Cardiology (TSOC) for the management of ST-segment elevation	▪ A 12-lead ECG should be performed and shown to an emergency medicine physician within 10 minutes of ED arrival. ▪ The time delay from patient arrival at the ED to balloon inflation in the PCI should be less than 90 minutes; alternatively, if thrombolytic therapy is chosen, the door-to-needle time should be

Organisation(s), Country/region (year)	Title	Recommendation(s)
	myocardial infarction	less than 30 minutes.
Europe		
BSC, Belgium (2010)	Implementation of reperfusion therapy in ST Segment Elevation Myocardial Infarction (STEMI). a policy statement from the Belgian Society of Cardiology and its working group of acute cardiology and interventional cardiology	▪ A cardiac evaluation must be done within 20 min ▪ If the primary percutaneous transluminal coronary angioplasty option is preferred, the treatment must be done quickly (door-to-balloon: <90 ± 30 minutes) ▪ If thrombolytic therapy is selected, the infusion should be within 30 minutes from the admission (door-to-drug time <30 min)
ESC, Europe (2011)	Pre-hospital treatment of STEMI patients. A scientific statement of the Working Group Acute Cardiac Care of the European Society of Cardiology	**Primary PCI:** ▪ within 120 min from FMC (or within 90 min, when FMC is 2 h from the onset of symptoms) — ≤90 min for early (<2 h) presenters with large viable myocardium and low bleeding risk
ERC, Europe (2015)	European Resuscitation Council Guidelines for Resuscitation 2015 Section 8. Initial management of acute coronary syndromes	▪ Patients presenting with STEMI in the emergency department of a non-PCI capable hospital should be transported immediately to a PCI centre provided that treatment delays for PPCI are less than 120 min (60 to 90 min for early presenters and those with extended infarctions), otherwise patients should receive fibrinolysis and be transported to a PCI centre. ▪ When fibrinolysis is the planned treatment strategy, we recommend using pre-hospital fibrinolysis in comparison to in-hospital fibrinolysis for STEMI where transport times are >30 min and pre-hospital personnel are well trained.
ESC, Europe (2017)	2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation	▪ For patients presenting in a non-PCI centre, door-in to door-out time, defined as the duration between arrival of the patient at the hospital to discharge of the patient in an ambulance en route to the PCI centre, is a new clinical performance measure, and ≤30 minutes is recommended to expedite reperfusion care. ▪ Maximum time from FMC to ECG and diagnosis <=10 min ▪ Maximum expected delay from STEMI diagnosis to primary PCI (wire crossing) to choose primary PCI strategy over fibrinolysis (if this time cannot be met, consider fibrinolysis) <=120 mins ▪ Maximum time from STEMI diagnosis to wire crossing in patients presenting at primary PCI

Organisation(s), Country/region (year)	Title	Recommendation(s)
		hospitals <=60 min ▪ Maximum time from STEMI diagnosis to wire crossing in transferred patients <=90 min
SIGN, Scotland (2016)	Acute coronary syndrome	▪ When primary percutaneous coronary intervention cannot be provided within 120 minutes of ECG diagnosis, patients with an ST-segment-elevation acute coronary syndrome should receive immediate (prehospital or admission) thrombolytic therapy. ▪ Primary PCI is the recommended reperfusion therapy over fibrinolysis if performed by an experienced team within 120 minutes of first medical contact but that the target for quality assessment should be provision of primary PCI within 90 minutes of first medical contact.
Socialstyrelsen, Sweden (2018)	National guidelines for cardiac care	▪ If the treatment can be administered in reasonable time, PCI is the first step for myocardial infarction with ST elevation. Healthcare and medical treatment should however be able to offer thrombolysis within 30 minutes after the ECG for those cases where primary PCI is not available within 120 minutes.
NICE, UK (2013)	Myocardial infarction with ST-segment elevation: acute management	▪ Offer coronary angiography, with follow-on primary PCI if indicated, as the preferred coronary reperfusion strategy for people with acute STEMI if: – Presentation is within 12 hours of onset of symptoms and – Primary PCI can be delivered within 120 minutes of the time when fibrinolysis could have been given.
NICE, UK (2014)	Acute coronary syndromes in adults [QS68]	▪ Adults with acute STEMI who present within 12 hours of onset of symptoms have primary PCI, as the preferred coronary reperfusion strategy, as soon as possible but within 120 minutes of the time when fibrinolysis could have been given.
North America		
CVHNS, Canada (2008)	Nova Scotia Guidelines for Acute Coronary Syndromes	▪ Obtain a standard 120lead ECG within 10 minutes of first medical contact. ▪ If the time from first medical contact to balloon inflation for primary PCI is estimated to be > 90 minute, prompt thrombolysis is the preferred reperfusion strategy. ▪ Primary PCI should be considered for other acute STEMI patients, provided there is a high likelihood of balloon inflation within 90 minutes of first medical contact and within 12 hours of symptom onset. ▪ For patients who require transportation, the maximum time from first medical contact to arrival at the cardiac catheterization laboratory should ideally not exceed 60 minutes. ▪ Acute STEMI patients who present to a facility without access to primary PCI within 90 minutes of first diagnostic ECG should receive thrombolytic therapy with a target door to needle time of ≤30 minutes unless contraindicated.

Organisation(s), Country/region (year)	Title	Recommendation(s)
CCN, Canada (2014)	Quality-Based Procedures Clinical Handbook for Coronary Artery Disease	▪ Primary PCI is the recommended reperfusion strategy with a goal of 90 minutes or less from first medical contact to device (balloon) inflation. ▪ However, if fibrinolytic therapy is chosen as the reperfusion strategy, it should be administered within 30 minutes of hospital arrival. ▪ Fibrinolytic therapy is recommended when there is an anticipated delay of greater than 120 minutes to performing primary PCI. ▪ For STEMI patients who initially arrive at a non-PCI capable centre, immediate EMS transfer to a PCI-capable hospital is recommended with FMC to device time goal of 120 minutes or less.
CCS/CAIC, Canada (2019)	2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the Acute Management of ST-Elevation Myocardial Infarction: Focused Update on Regionalization and Reperfusion	▪ FMC to diagnosis (ECG acquisition and interpretation): ≤10 minutes ▪ Diagnosis to catheterization lab activation: ≤10 minutes ▪ Door-in to door-out time for emergency departments: ≤30 minutes ▪ Transport times for interfacility transfers or STEMI patients diagnosed in the field: ≤60 minutes ▪ Time from arrival at catheterization lab to first device activation: ≤30 minutes ▪ Total time from FMC to first device activation (for primary PCI) – For non-PCI centres or patients diagnosed in the field: ≤120 minutes – For patients presenting to PCI centres: ≤90 minutes ▪ Time from FMC to fibrinolysis: ≤30 minutes
Partners HealthCare, USA (2008)	Guidelines for therapy of ST-segment-elevation acute myocardial infarction in patients presenting to partners healthcare system hospital emergency departments	▪ ECG is performed and read by attending Emergency Physician within 10 minutes of hospital arrival ▪ If PCI cannot be available within 90 minute door-to-balloon window, Emergency Physician attending may opt for stat intravenous fibrinolysis
AHA, USA (2015)	2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care – Part 9: Acute coronary syndromes:	▪ PPCI is the preferred reperfusion strategy when time from symptom onset is less than 12 hours and time to PPCI from first medical contact in these patients is anticipated to be less than 120 minutes. Regardless of whether time of symptom onset is known, the interval between first medical contact and reperfusion should not exceed 120 minutes ▪ In STEMI patients presenting within 2 hours of symptom onset, immediate fibrinolysis rather than PPCI may be considered when the expected delay to PPCI is more than 60 minutes ▪ In STEMI patients presenting within 2 to 3 hours after symptom onset, either immediate

Organisation(s), Country/region (year)	Title	Recommendation(s)
		fibrinolysis or PPCI involving a possible delay of 60 to 120 minutes might be reasonable ▪ In STEMI patients presenting within 3 to 12 hours after symptom onset, performance of PPCI involving a possible delay of up to 120 minutes may be considered rather than initial fibrinolysis ▪ If PCI is the chosen method of reperfusion for the prehospital STEMI patient, it is reasonable to transport patients directly to the nearest PCI facility, bypassing closer EDs as necessary, in systems where time intervals between first medical contact and balloon times are <90 minutes and transport times are relatively short (i.e., <30 minutes) ▪ If the patient has STEMI, the goals of reperfusion are to provide PCI within 90 minutes of arrival (90-minute interval 'door-to-balloon')
ACEP, USA (2017)	Clinical Policy: Emergency Department Management of Patients Needing Reperfusion Therapy for Acute ST-Segment Elevation Myocardial Infarction	▪ Fibrinolytics may be administered to patients when door-to-balloon time is anticipated to exceed 120 minutes.
AHA/ACC, USA (2017)	2017 AHA/ACC Clinical Performance and Quality Measures for Adults With ST-Elevation and Non–ST-Elevation Myocardial Infarction	**Acute STEMI** ▪ Time to Primary PCI – Primary PCI during the hospital stay with a time from FMC-to device time ≤90 min ▪ Time From ED Arrival at STEMI Referral Facility to ED Discharge From STEMI Referral Facility in Patients Transferred for Primary PCI – Time from the ED arrival at STEMI referral facility to ED discharge from STEMI referral facility is ≤30 min ▪ Time to Primary PCI Among Transferred Patients: – Time from FMC (at or before ED arrival to the STEMI referral facility [e.g., non–PCI-capable facility]) to primary PCI at the STEMI receiving facility (PCI-capable facility) is ≤120 min
South America		
SBC, Brazil (2015)	Telecardiology guideline for the care of patients with acute coronary syndrome and other heart diseases	▪ If the STEMI patient can be transported to a hospital with PCI capability and the PCI can be performed within 120 minutes, or if the patient has contraindication to fibrinolytic treatment, the patient must be transported to the hospital with PCI. ▪ In the Remote Care Unit, all patients with chest pain must have a 12-lead electrocardiogram performed, which should be interpreted in less than 10 minutes from the FMC.
SBC, Brazil (2015)	V Guideline of the Brazilian	▪ Administration of fibrinolytics when it is not possible to perform primary PCI or expectation of

Organisation(s), Country/region (year)	Title	Recommendation(s)
	Society of Cardiology on Acute Myocardial Infarction Treatment with ST Segment Elevation	FMC-to-balloon time> 120 minutes for hospital with PCI centre ▪ FMC-to-ECG = 10 minutes ▪ FMC-to-fibrinolysis = 30 minutes ▪ FMC-to-primary PCI = – 90 minutes (PCI centre) – 120 minutes (non-PCI centre)
SBC, Brazil (2017)	Guidelines of the Brazilian Society of Cardiology and the Brazilian Society of Hemodynamics and Interventional Cardiology on Percutaneous Coronary Intervention	▪ Primary PCI should be performed with balloon time <90 minutes, but ideally <60 minutes ▪ Primary PCI is the preferred reperfusion strategy if center with primary PCI <120 minutes

ACC – American College of Cardiology; ACEP – American College of Emergency Physicians; ACS – acute coronary syndrome; ACSQHC – Australian Commission on Safety and Quality in Health Care; AHA – American Heart Association; AMM – Academy of Medicine Malaysia; ANZCOR – Australian and New Zealand Committee on Resuscitation; API – Association of Physicians of India; BCS – Belgian Society of Cardiology; CAIC – Canadian Association of Interventional Cardiology; CCN – Cardiac Care Network of Ontario; CCS – Canadian Cardiovascular Society; CSI – Cardiological Society of India; CVHNS – Cardiovascular Health Nova Scotia; DNT –door-to-needle time; DBT – door-to-balloon time; ECG – electrocardiogram; ED – emergency department; ERC – European Resuscitation Council; ESC – European Society of Cardiology; FMC – first medical contact; MOH – Ministry of Health Malaysia; NHAM – National Heart Association of Malaysia; NHFA – National Heart Foundation of Australia; NICE – National Institute for Health and Care Excellence; PCI – percutaneous coronary intervention; PPCI – primary percutaneous coronary intervention; SBC – Brazilian Society of Cardiology; SIGN – Scottish Intercollegiate Guidelines Network; Socialstyrelsen – The Swedish National Board of Health and Welfare; STEMI – ST-elevation myocardial infarction; TSOC – Taiwan Society of Cardiology

Table A.21: Guidance documents making recommendations about specific procedures/conditions or new PCI centres

Organisation(s), Country/region (year)	Title	Recommendation(s)
Asia-Pacific		
CSI, India (2018)	Transradial access for coronary diagnostic and interventional procedures: Consensus statement and recommendations for India: Advancing Complex CoronariES Sciences through TransRADIAL intervention in India – ACCESS RADIAL™: Clinical consensus recommendations in collaboration with Cardiological Society of India (CSI)	**Institutional facilities** ▪ Radial lounge facility* should be promoted as it enhances the comfort and recovery of the patient. **Operator volume** ▪ A caseload of at least 80 cases/operator in a year.
Europe		
Euro CTO Club, Europe (2012)	Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club	**Operator volume** ▪ The minimal number of 50 CTOs per year to maintain competency translates into a model where only a limited number of operators and centres should perform CTO treatment.
EAPCI/ESC, Europe (2013)	Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European	**Institutional facilities** ▪ A dedicated board connected to the cath lab table for the left and right arm should be available. **Operator volume** ▪ To achieve the best results in TRI, individual operators and institutional teams should aim at maintaining the highest feasible rate of TRI. However, a reasonable objective for achieving an

Organisation(s), Country/region (year)	Title	Recommendation(s)
	Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care and Thrombosis of the European Society of Cardiology	average satisfactory proficiency is aiming, after the learning curve has been completed, for over 50% radial access in routine practice with a minimum of 80 procedures/year per operator (including diagnostic and interventional procedures).
ACCA (ESC), Europe (2017)	Editor's Choice-The organization of chest pain units: Position statement of the Acute Cardiovascular Care Association	**Institutional facilities** ▪ CPUs** can be integrated into an ED with predefined continuous availability of 2–4 monitoring beds dedicated to chest pain patients. Available in hospital (365 day/24 h) or with pre-defined transfer protocol to hospital with PCI facilities. ▪ For more advanced CPU settings, a separate department adjacent to the ED is advisable. Such a department should contain at least four monitoring beds as well as a diagnostic/treatment room and a waiting room. Available in the hospital / 365 day/24 h. ▪ Permanent access to heart catheterization and PCI facilities should be possible. If a catheterization lab is not present at the hospital, predefined transfer protocols to a hospital with PCI facilities should be present and operational. This protocol includes the permanent availability of an intensive care mobile unit to transfer critically ill patients (cf. STEMI) to a PCI hospital. ▪ Technical requirements: – ECG with 12-lead monitoring – Heart rhythm, blood pressure and pulse oximetry monitoring equipment – A resuscitation set with a defibrillator – A transcutaneous pacing modality should be available on the external defibrillator. – Cardiac biomarkers: 24-h emergency laboratory with turnaround time of <90 min (<60 min at advanced CPUs). If this cannot be achieved, point-of-care methods should be considered. – Beyond cardiac biomarkers, a general laboratory set containing electrolytes, renal and liver function, C-reactive protein and D-dimer should be available with turn-around times of <60 min. – Chest X-ray – Transthoracic echocardiography – Ultrasound equipment – A blood gas analysis machine

Organisation(s), Country/region (year)	Title	Recommendation(s)
		– Non-invasive ventilation and transport ventilator – Transport monitoring **Staffing levels** ▪ The medical staff should be supported by at least one nurse per four beds, who is dedicated to CPU/emergency/CCU. **Time/Distance to treatment** ▪ For STEMI patients, an urgent invasive evaluation is recommended with a target door-in–door-out time < 30 min if the patient needs to be transferred to a PCI centre and with a target door-to-balloon time of < 60 min if a catheterization lab is present on site. **Monitoring of standards** ▪ Quality monitoring should be organized to measure and evaluate operational performance and adherence to evidence-based guidelines. Predefined quality measures can be extracted from hospital-based patient files. Participation in a specific CPU registry (local or supra-regional) with more continuous quality assessment is recommended for advanced level CPUs.
North America		
SCAI, USA (2014)	Best practices for transradial angiography and intervention: A consensus statement from the society for cardiovascular angiography and intervention's transradial working group	**Operator volume** ▪ Operators and sites should not start performing transradial primary PCI until they have performed at least 100 elective PCI cases with a 'radial first' approach and their femoral crossover rate is ≤4%. **Monitoring and Standards** ▪ Door-to-balloon times should be monitored closely when starting a transradial primary PCI programme and cases with times that extend beyond recommended benchmarks should be reviewed to identify whether the radial approach was responsible for the delay.
New PCI Centre Europe		
BCIS, UK (2015)	Statement on the Development and Peer Review of New PCI Services	▪ The plan for a new PCI service should ensure that the service will be compliant with BCIS Guidance. It is recognised that a new PCI service may not meet all BCIS Guidance from inception and a development period of defined duration should be explicitly included in the planning process. New PCI services should be fully compliant with BCIS Guidance within three years. **Institutional facilities**

Organisation(s), Country/region (year)	Title	Recommendation(s)
		▪ Hospitals planning a PCI service must be experienced in the management of haemodynamically unstable patients including the use of echocardiography, inotropic support, intra-aortic balloon counterpulsation, invasive haemodynamic monitoring, and temporary pacing. Hospitals must have ready access to intensive care facilities, transfusion services, renal support and vascular surgery. ▪ At least one dedicated cardiac catheter laboratory with high quality digital imaging, including freeze frame, zoom, road mapping, and immediate playback capability. In hospitals with only one catheter laboratory a high resolution portable fluoroscopy unit should be available to allow safe completion of a PCI procedure if the primary radiographic equipment fails. ▪ Appropriate radiation protection equipment including lead aprons and screens. ▪ High quality physiological measurement equipment. ▪ Oxygen saturation monitoring. ▪ PCI consumables including a range of guide catheters, wires, balloons, stents (bare metal and drug-eluting), covered stents, other equipment (e.g. embolic protection devices), and adjunctive pharmacological agents (e.g. glycoprotein IIb/IIIa receptor antagonists) as appropriate to the intended case-mix. ▪ An intra-aortic balloon pump, which should be available for all PCI procedures (a second balloon pump allows the service to continue if the first balloon pump is in use). ▪ Facilities for cardiopulmonary resuscitation and management of haemodynamically unstable patients, including access to urgent transthoracic echocardiography, pericardial aspiration, and anaesthetic support. ▪ Pre- and post-procedural patient preparation and monitoring areas including facilities for cardiac rhythm, oxygen saturation, and arterial pressure monitoring. ▪ Digital archive for storage and retrieval of coronary arteriographic images. ▪ IT and audit infrastructure (hardware, software, personnel) to ensure complete data submission on all PCI procedures to the National Congenital Heart Disease Audit (NCHDA), and to support institutional and regional audit of PCI activity. ▪ Provision of optimal patient care requires continuous (24 hour, 7 days per week) local consultant interventional cardiologist cover and continuous access to the local catheter laboratory after all PCI procedures. All PCI services should develop plans to provide this level of service within three years. ▪ For elective PCI: As a minimum, all PCI services must provide access to the local catheter laboratory for six hours after routine working hours (9am to 5pm) and after completion of all elective PCI procedures. The laboratory should be fully operational within 60 minutes of a call. Complications

Organisation(s), Country/region (year)	Title	Recommendation(s)
		more than six hours after elective PCI are infrequent but may require emergency catheter laboratory access, and continuous (24 hour, 7 days per week) access to the local catheter laboratory therefore provides optimal patient care. If uninterrupted access to the local catheter laboratory cannot be provided, arrangements for emergency transfer of a patient to another PCI service providing continuous catheter laboratory access must be agreed in writing between all relevant parties. All PCI services should develop plans for continuous (24 hour, 7 days per week) access to the local catheter laboratory. ▪ For urgent PCI: PCI services managing patients with non-ST elevation acute coronary syndrome should provide continuous (24 hour, 7 days per week) local consultant interventional cardiologist cover and continuous local catheter laboratory access. Plans to establish an uninterrupted service should be apparent at the inception of the new PCI service. ▪ For urgent PCI: If a continuous local service cannot be provided (for instance, during the development phase of a new service), there should be access to the local catheter laboratory for an absolute minimum of six hours after routine working hours (9am to 5pm) and after completion of the last PCI procedure. ▪ For primary PCI: Primary PCI patients require specialist cardiology care and may need re-intervention in the catheter laboratory on an urgent or emergency basis. Optimal care of primary PCI patients requires continuous (24 hour, 7 days per week) consultant interventional cardiologist cover and catheter laboratory access at the hospital where the primary PCI is carried out. ▪ For primary PCI: In some cardiac care networks in the UK some hospitals contributing to primary PCI services may operate a restricted hours service for logistic, geographic, or other reasons. If a continuous local primary PCI service cannot be provided, robust arrangements for management of patients requiring reperfusion therapy outside of local operating hours must be developed in collaboration with all other relevant stakeholders. In addition there must be robust arrangements for the care of primary PCI patients treated at the hospital offering a restricted hours primary PCI service throughout the patients' admission to that hospital. These arrangements must be agreed with relevant stakeholders as part of a network-wide primary PCI service strategy and must include continuous (24 hour, 7 days per week) consultant interventional cardiologist cover and uninterrupted access to a catheter laboratory. **Institutional Volume** Total PCI volume ▪ It has been suggested that the relationship between volume and outcome has been harder to

Organisation(s), Country/region (year)	Title	Recommendation(s)
		demonstrate since the introduction of coronary stents into routine practice, particularly for elective PCI. The available evidence suggests that the volume-outcome relationship is strongest for patients at highest risk of adverse outcomes, including patients with non-ST and ST-elevation acute coronary syndromes. ▪ All new PCI services should therefore plan to carry out at least 200 therapeutic coronary interventions in the first year and increase activity to at least 400 cases per annum within three years. Instrumentation of a coronary artery for diagnostic purposes (e.g. with a pressure wire or intravascular ultrasound catheter) should not be included in this number of interventions. If the local catchment population is unlikely to require 400 cases per annum there should be other explicit imperatives that justify the development of the new PCI service (e.g. long distance to the nearest alternative PCI service). **Primary PCI volume** ▪ Hospitals carrying out at least 50 primary PCI procedures for ST-elevation myocardial infarction per annum may achieve better outcomes than services carrying out fewer procedures. High total institutional PCI volume (more than 400 PCI cases per annum) has been associated with short door to balloon times and lower hospital mortality for patients undergoing primary PCI. ▪ In the United Kingdom there are approximately 500 reperfusion-eligible myocardial infarction patients per million population per annum. If an individual United Kingdom hospital provides an independent and continuous (24 hour, 7 days per week) primary PCI service (with an appropriate number of medical and non-medical staff to cover a rota) the hospital would need to serve a population of at least 200 000 to achieve a minimum number of 100 primary PCI procedures per annum. ▪ Notwithstanding ESC and ACC/AHA guidance, in some cardiac care networks in the United Kingdom primary PCI services are provided by a group of hospitals, including some hospitals that offer primary PCI during restricted hours. Individual hospitals participating in a primary PCI service should be able to maintain a level of activity that will ensure institutional competence in dealing with unselected patients with ST-elevation myocardial infarction. If a single hospital provides primary PCI during normal daytime working hours only (for example, Monday to Friday, 9am to 5pm) and wishes to carry out a minimum of 100 on-site primary PCIs per annum it would need to serve a population of approximately 500 000. ▪ An individual hospital contributing to a primary PCI service must be part of the network-wide primary PCI strategy to ensure that all patients with ST-elevation myocardial infarction have

Organisation(s), Country/region (year)	Title	Recommendation(s)
		equitable, continuous (24 hour, 7 days per week), and effective access to primary PCI, regardless of the time of presentation. **Operator Volume** ▪ Independent operators must carry out at least 75 PCI cases as primary operator per annum to maintain competence. ▪ PCI operators who carry out fewer than 75 primary operator procedures per annum, and operators who work on more than one site but will contribute fewer than 50 cases per annum to the new service, should not form part of the team of three independent operators at the new PCI site. ▪ Primary PCI services are unlikely to be sustainable with fewer than five operators and operators carrying out at least 20 primary PCI procedures per annum have been reported to have lower in-hospital mortality than operators doing fewer primary PCI procedures. ▪ Operators who carry out primary PCI at hospitals with lower institutional primary PCI volumes would need to participate in a regional primary PCI rota to maintain individual operator volumes of 20 primary PCI procedures per annum. **Surgical cover** ▪ In contemporary PCI practice haemodynamic or ischaemic complications requiring emergency cardiac surgery occur infrequently. Nevertheless, guidance from BCIS and other national societies states that emergency cardiac surgical cover is required for PCI. ▪ All new PCI services must agree a written protocol for the provision of emergency cardiac surgical cover with a local cardiac surgical service. This requirement applies to PCI services at hospitals with and without on-site cardiac surgery. The protocol must describe clear lines of communication between the PCI service and the cardiac surgical service, and must ensure that surgical cover is available for all relevant PCI procedures. ▪ Case selection for PCI should take account of the potential need for and access to emergency cardiac surgery. For example, it may not be appropriate to treat high risk patients who are also candidates for emergency surgical revascularization in hospitals without on-site cardiac surgery. ▪ PCI services without on-site cardiac surgery must agree a written protocol with the local ambulance service that describes arrangements for emergency transfer of patients to the cardiac surgical service. The protocol must include transfer of patients with an intra-aortic balloon pump and should be tested with a trial transfer. ▪ All PCI services must establish a mechanism for interaction with the local cardiac surgical service,

Organisation(s), Country/region (year)	Title	Recommendation(s)
		including discussion of complex cases within the framework of a regular multi-disciplinary meeting. Where appropriate such multi-disciplinary case discussions should be facilitated by electronic image transfer and video conferencing. ▪ The time between a decision to refer a patient for emergency cardiac surgery and cardiopulmonary bypass being established should be as short as possible and less than 90 minutes. **Staffing levels** ▪ The provision of a high quality PCI service requires an experienced multidisciplinary team capable of delivering high quality care throughout the patient pathway, including pre-procedural assessment, consent, intervention, post-procedural care, and rehabilitation. ▪ Provision of optimal patient care requires continuous (24 hour, 7 days per week) local consultant interventional cardiologist cover. ▪ For urgent PCI: PCI services managing patients with non-ST elevation acute coronary syndrome should provide continuous (24 hour, 7 days per week) local consultant interventional cardiologist cover and continuous local catheter laboratory access. Plans to establish an uninterrupted service should be apparent at the inception of the new PCI service. ▪ For primary PCI: Primary PCI patients require specialist cardiology care and may need re-intervention in the catheter laboratory on an urgent or emergency basis. Optimal care of primary PCI patients requires continuous (24 hour, 7 days per week) consultant interventional cardiologist cover and catheter laboratory access at the hospital where the primary PCI is carried out. ▪ In addition there must be robust arrangements for the care of primary PCI patients treated at the hospital offering a restricted hours primary PCI service throughout the patients' admission to that hospital. These arrangements must be agreed with relevant stakeholders as part of a network-wide primary PCI service strategy and must include continuous (24 hour, 7 days per week) consultant interventional cardiologist cover and uninterrupted access to a catheter laboratory. ▪ All PCI services should have at least three independent PCI operators to ensure that an uninterrupted service can be provided. An independent PCI operator is someone who has successfully completed a United Kingdom (or equivalent) training programme in PCI and is on the Specialist Register for cardiology. An independent operator decides that PCI is appropriate management, plans the intervention strategy, and carries out the procedure without supervision. A service with only three independent operators may be difficult to sustain long-term and services should plan to increase the number of operators to four to six, depending on workload. ▪ When new PCI services start, some fully trained PCI operators may wish to resume coronary

Organisation(s), Country/region (year)	Title	Recommendation(s)
		interventional practice after a period of low volume activity or a period of absence from coronary interventional practice. Operators who have carried out 75 cases per year for the previous two years but are then absent from coronary interventional practice for less than 6 months (for example illness, pregnancy, temporary suspension, etc.) do not require additional training before resuming independent practice. If the period of absence exceeds 6 months but is less than two years the operator is advised to carry out a minimum of 20 cases with the support of an independent operator colleague before resuming fully independent practice. Operators who have been fully trained but have not maintained 75 cases per annum for two years or more are advised to spend two years performing at least 75 cases per annum under the supervision of an independent operator before resuming independent practice. ▪ Cardiologists who have never been fully trained in PCI and who wish to start PCI must undergo formal PCI training. ▪ New PCI services must be supported by a range of other clinical staff with relevant nursing, radiography and physiology expertise. Formal training opportunities for non-medical staff are limited, but the non-medical clinical team must have sufficient experience in PCI to ensure safe and effective PCI service delivery. The number of non-medical staff will depend on work load and local practice but should be sufficient to sustain the service, including requirements for out-of-hours rotas. ▪ On call rotas: All independent PCI operators should be involved in the care of, and share responsibility for PCI patients throughout the patient pathway. Arrangements for on-call rotas must be sustainable and agreed locally between all independent PCI operators contributing to the PCI service. On-call rotas may include participation in a primary PCI service. This can be achieved by local institutional or regional out-of-hours rotas. These arrangements must be explicit, robust, and formally agreed in writing between all participating operators and hospitals. ▪ For elective PCI: As a minimum, a consultant interventional cardiologist must be available on a formal on-call rota to provide overnight medical cover after all elective PCI procedures, including day-case procedures. The rota should be published and formally agreed between all participating cardiologists. The rota must cover days when elective PCI is carried out at the PCI site, but all services should develop plans for continuous (24 hour, 7 days per week) consultant interventional cardiologist cover. **Monitoring of standards and or KPIs** ▪ All new PCI services must submit complete procedural and in-hospital outcome data to NCHA. This

Organisation(s), Country/region (year)	Title	Recommendation(s)
		includes the recording of all major adverse cardiovascular and cerebrovascular events up to hospital discharge. These data will be used to assess the quality of individual PCI services using a range of metrics, including risk-adjusted outcomes, and call to balloon and door to balloon times for patients undergoing primary PCI. ▪ All PCI services should formally audit local PCI activity at least annually, but more frequent audit may be appropriate, particularly during the development phase of a new PCI service. All services should develop plans for participation in regional audit and peer review with colleagues from other PCI centres and from the local surgical service. ▪ All institutions providing a primary PCI service should participate in the national audit programme and provide outcomes of all primary PCI patients to the point of hospital discharge. Analysis of these audit data and further clinical research may influence the future provision of services.

ACCA – Acute Cardiovascular Care Association; CCU – coronary care unit; CPU – chest pain unit; CSI – Cardiological Society of India; CTO – chronic total occlusion; EAPCI – European Association of Percutaneous Cardiovascular Interventions; ECG – electrocardiogram; ED –emergency department; ESC – European Society of Cardiology; PCI – percutaneous coronary intervention; SCAI – Society for Cardiovascular Angiography and Interventions; STEMI – ST-elevation myocardial infarction; TRI – transradial intervention.

*Radial lounge is a dedicated facility that is able to accommodate patients in an attractive environment that minimizes the feeling of 'hospitalization' and enhances the recovery of the patients as well as reduces the need of the hospital beds

**Chest pain units are defined as organizational short stay units with specific management protocols designed to facilitate and optimize the diagnosis of patients presenting with chest pain in the emergency department

Appendix 6 — Studies excluded after full-text review

Table A.22: Table of studies excluded after full-text review (RQ1)

Study	Reason for exclusion
Adornato E, Pimpinella A, Adornato EMF. Management for chronic heart failure patients between territory and hospital: The MESPE project. Mediterranean Journal of Pacing and Electrophysiology. 2011;13(1-2):28-30.	Full text unobtainable
Agency for Clinical Innovation - New South Wales G. State Cardiac Reperfusion Strategy (SCRS). 2019;2019	Editorial or Commentary
Albert A, Born F, Kamiya H, Saeed D, Akhyari P, Kindgen-Milles D, et al. Mobile extracorporeal life support for patients with refractory cardiogenic shock or reanimation - The concept of a regional supply network. Circulation. 2012;126(21).	Conference abstract
Alberta Health S. Heart Failure Network - A System Wide Approach to Chronic Heart Failure Care.2018(23 March).	Unreliable source
Anderson LL, French WJ, Peng SA, Vora AN, Henry TD, Roe MT, et al. Direct Transfer From the Referring Hospitals to the Catheterization Laboratory to Minimize Reperfusion Delays for Primary Percutaneous Coronary Intervention: Insights From the National Cardiovascular Data Registry. Circ Cardiovasc Interv. 2015;8(9):e002477.	No evidence of cardiac clinical network
Andriantoro H, Sunu I, Dharma S, Dakota I, Sukmawan R, Siswanto BB, et al. No sex disparities of reperfusion therapy for STEMI patients admitted to a tertiary care academic hospital. European Heart Journal: Acute Cardiovascular Care. 2016;5:197.	Conference abstract
Arnold M, Kaan AM, Howlett J, Ignaszewski A, LeBlanc MH, Liu P, et al. Specialized heart failure outpatient clinics: What staff are required, what is their workload, and can these data facilitate the planning of new heart failure clinics? J Card Fail. 2011;17(8):S109.	Conference abstract
Ascencio Lemus MG, Iglesias Garriz I, Prieto Salvador I, Del Castillo Garcia S, Alonso Orcajo N, Lezcano Pertejo C, et al. Short-term mortality on ST-segment myocardial infarction after the implementation of a rapid access system to reperfusion. Eur Heart J. 2017;38:588-9.	Conference abstract
Aspromonte N, Gulizia MM, Di Lenarda A, Mortara A, Battistoni I, De Maria R, et al. [ANMCO/SIC Consensus document: The heart failure network: organization of outpatient care]. G Ital Cardiol (Rome). 2016;17(7-8):570-93.	Duplicate study;
Aspromonte N, Gulizia MM, Di Lenarda A, Mortara A, Battistoni I, De Maria R, et al. ANMCO/SIC Consensus Document: cardiology networks for outpatient heart failure care. Eur Heart J Suppl. 2017;19(Suppl D):D89-d101.	No evidence of cardiac clinical network
Assyag P, Thébaut JF, Ziccarelli C, Cohen A. Therapeutic education and multidisciplinary approaches in heart failure. Medecine Therapeutique - Cardio. 2008;4(1):79-87.	No evidence of cardiac clinical network
Azevedo PM, Bispo J, Carvalho D, Guedes J, Bento D, Pereira S, et al. Are we choosing the right reperfusion therapy in early presenters with ST-segment elevation myocardial infarction? Eur Heart J. 2017;38:989.	Conference abstract
Azzalini L, Sole E, Sans J, Duran A, Vila M, Garcia-Moll X, et al. Feasibility and safety of an early discharge strategy after low-risk acute myocardial infarction treated with primary coronary percutaneous intervention: A pilot study. European Heart Journal: Acute Cardiovascular Care. 2013;2:19-20.	Focus is on changes to in-hospital protocols that are not related to cardiac clinical network formation
Babic Z, Heitzler VN, Milicic D, Bergovec M, Raguz M, Mirat J, et al. Is it door-to balloon time really important? European Heart Journal, Supplement. 2010;12:F65.	Conference abstract
Bach DS. [Commentary on] Clinical impact of an inter-hospital transfer strategy in patients with ST-elevation myocardial infarction undergoing primary angioplasty: the Emilia-Romagna ST-Segment Evaluation Acute Myocardial Infarction Network. ACC Cardiosource Review Journal. 2008;17(9):41-.	Conference abstract

Study	Reason for exclusion
Bagai A, Granger CB. Regionalization of ST-segment elevation myocardial infarction care: a task unfinished. Am Heart J. 2012;164(5):633-5.	Editorial or Commentary
Emergency department bypass for ST-Segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: a report from the American Heart Association Mission: Lifeline program. Circulation. 2013;128(4):352-9.	Research networks, Information Networks, Communities of Practice, or Studies that utilised clinical networks to obtain samples for their study
Bagai A, Al-Khalidi HR, Sherwood MW, Munoz D, Roettig ML, Jollis JG, et al. Regional systems of care demonstration project: Mission: Lifeline STEMI Systems Accelerator: design and methodology. Am Heart J. 2014;167(1):15-21.e3.	Inadequate information
Bagai A, Jollis JG, Dauerman HL, Peng SA, Rokos IC, Bates ER, et al. Bagai A, Dangas GD, Stone GW, Granger CB. Reperfusion strategies in acute coronary syndromes. Circ Res. 2014;114(12):1918-28.	Review
Baldazzi F, Santarelli A, Marzaloni S, Masini V, Franco N, Ruffini M, et al. Systematic data feedback of primary pci network: Impact on delay reperfusion. G Ital Cardiol. 2012;13(5):101S.	Conference abstract
Barn K, Akram MMA, Blankenship J, Stout CB, Carey D, Sun H, et al. Impact of pre-hospital ECG on time to treatment and clinical outcome in a rural regional STEMI network. J Am Coll Cardiol. 2013;61(10):E114.	Conference abstract
Baruch T, Rock A, Koenig WJ, Rokos I, French WJ. 'Call 911' STEMI protocol to reduce delays in transfer of patients from non primary percutaneous coronary intervention referral Centers. Crit Pathw Cardiol. 2010;9(3):113-5.	Focus is on changes to Emergency Medical Services protocols (e.g. ambulance by-pass protocols) that are not related to cardiac clinical network formation
Battistoni I, Pini D, DeMaria R, Iacoviello M, Mortara A, Navazio A, et al. Distribution and organization of heart failure outpatient clinics in Italy: Preliminary data from the national working group survey. Eur J Heart Fail. 2016;18:94.	Conference abstract
Bayeff-Filloff M, Pawlak CL, Prückner S. Networked emergency care for hospitals of various care levels. Notfall und Rettungsmedizin. 2014;17(3):202-8.	No evidence of cardiac clinical network
Beardsall M. Initiating a regional heart failure strategy: Translating guidelines into practice. Canadian Journal of Cardiology. 2010;26:149D.	Conference abstract
Belle L, Labarere J, Ageron FX, Savary D, Debaty G, Barone-Rochette G, et al. Does a regional system of care impact on reperfusion strategies in ST-segment elevation myocardial infarction? Eur Heart J. 2012;33:142.	Conference abstract
Benedek IS, Jako B, Benedek T. Impact of logistic network organization in reduction of STEMI mortality in an unselected population from central romania. Eur Heart J. 2012;33:146-7.	Conference abstract
Benedek T, Balazs B, Jako B, Rat N, Benedek I. Distance-related differences in critical times, protocol activation and mortality in a regional STEMI network. Eur Heart J. 2014;35:1171-2.	Conference abstract
Benedek T, Gyongyosi M. Out-of-Hospital Cardiac Arrest in Acute Myocardial Infarction and STEMI Networks. J Crit Care Med (Targu Mures). 2016;2(1):3-5.	Editorial or Commentary
Bernocchi P, Scalvini S, Tridico C, Borghi G, Zanaboni P, Masella C, et al. Healthcare continuity from hospital to territory in Lombardy: TELEMACO project. Am J Manag Care. 2012;18(3):e101-8.	No evidence of cardiac clinical network
Bhatia S, Anavekar NS, Al-Hijji M, Sims J, Barsness G, Singh M, et al. Elderly patients presenting with stemi appear to present later despite targeted protocols for expediting care. J Am Coll Cardiol. 2018;71(11).	Conference abstract

Study	Reason for exclusion
Birkemeyer R, Rillig A, Koch A, Miljak T, Soballa M, Benzing A, et al. ST-elevation acute myocardial infarction complicated by cardiogenic shock: Feasibility of area wide transfer PCI and impact on mortality in a regional network. American Journal of Cardiology. 2009;104(6):130D.	Conference abstract
Birkemeyer RG, Miljak T, Meyerfeldt U, Neuhaus M, Hildebrand D, Kohler H, et al. The off hours paradigm in primary percutaneous coronary intervention can be overcome by network structures. Eur Heart J. 2011;32:878.	Conference abstract
Birkemeyer RG, Schneider H, Rillig A, Kische S, Akin I, Paranskaya L, et al. Bypassing emergency rooms in primary PCI A comparison of two different network concepts. European Heart Journal: Acute Cardiovascular Care. 2013;2:129-30.	Conference abstract
Bonarek-Hessamfar M, Benchimol D, Lauribe P, Hadjo A, Matis P, Dartigues JF, et al. Multidisciplinary network in heart failure management in a community-based population: results and benefits at 2 years. Int J Cardiol. 2009;134(1):120-2.	Editorial or Commentary
Bonaventura K, Jander S, Fengler A, Hoffmann M, Franz W. Effect of strategies of business process management on door-to-balloon time in a regional network for the treatment of ST-segment elevation myocardial infarction. American Journal of Cardiology. 2009;104(6):121D.	Conference abstract
Bosson N, Eckstein M, Sung G, Koenig W, Kaji A, French W, et al. Survival and neurological outcome of out-of-hospital cardiac arrest in Los Angeles county: Preliminary results after regionalization of care. Circulation. 2012;126(21).	Conference abstract
Bowen ME, Roumie C, Minnick A, Donaghey B, Wilson AS, Fink CA, et al. A hub and satellite model to improve the quality of care for patients with congestive heart failure. J Gen Intern Med. 2012;27:S512-S3.	Conference abstract
Bradley S. Within the four walls and beyond: Trends in healthcare networking. Biomedical Instrumentation and Technology. 2008;42(6 SUPPL.):33-8.	No evidence of cardiac clinical network
Brezinov M, Kassam SA. Safety of primary PCI in a stand-alone PCI programme in ontario. Canadian Journal of Cardiology. 2011;27(5):S144-S5.	Conference abstract
British Columbia's Heart Failure N. History of BC's Heart Failure Strategy. 2019;2019(24 March).	Inadequate information
British Heart F. Integrated care pilots evaluation: final report. London: BHF, 2015.	No evidence of cardiac clinical network
Brooks SC, Scales D, Dainty K, Gray S, Pinto R, Racz E, et al. Post Arrest Consult Team: A knowledge translation strategy for post-cardiac arrest care. Critical Care. 2014;18:S178-S9.	Conference abstract
Brunetti ND, Dellegrottaglie G, Di Giuseppe G, De Gennaro L, Antonelli G, Di Biase M. Get your cardiologist wherever you want: Telecardiology supporting a regional EMS network (8 years and half a million ECGs). Eur Heart J. 2013;34:796.	Conference abstract
Burke MN, Solie C, Urbach J, Ramananda S, Ross M, Garberich R, et al. Influence of a standardized treatment protocol on patients with non-ST segment elevation myocardial infarction presenting to emergency departments. Catheterization and Cardiovascular Interventions. 2011;77:S21-S2.	Conference abstract
Cahuzac C, Ta TH, Henaoui A, Laborne FX, Briole N, Porche M, et al. Evaluation of the door in-door out (DIDO) time of acute coronary syndrome in hospitals without coronary care unit of the network RESSIF. Annales Francaises de Medecine d'Urgence. 2018;8(2):94-9.	No evidence of cardiac clinical network
Callaghan S, Mills J, Taylor B, Connor WO. A measurable clinical pathway for atrial fibrillation: what are the benefits for patients, clinicians, commissioners and cardiac networks? Heart. 2016;102:A36-A7.	Conference abstract
Caluza AC, Barbosa AH, Goncalves I, Oliveira CA, Matos LN, Zeefried C, et al. ST-Elevation myocardial infarction network: systematization in 205 cases reduced clinical events in the public health care system. Arq Bras Cardiol. 2012;99(5):1040-8.	Not in a high development index or EU country
Campana C, Monti L, Pirini S, Borghi G, Colombo C, Tavazzi L. [The homecare management of chronic heart failure followed up by hospital cardiologists: a pilot	No evidence of cardiac clinical network

Study	Reason for exclusion
study]. G Ital Cardiol (Rome). 2008;9(7):491-6.	
Carrillo JE, Carrillo VA, Guimento R, Mucaria J, Leiman J. The NewYork-Presbyterian Regional Health Collaborative: a three-year progress report. Health Aff (Millwood). 2014;33(11):1985-92.	No evidence of cardiac clinical network
Casella G, Scorcu G, Cassin M, Chiarella F, Chinaglia A, Conte MR, et al. Elderly patients with acute coronary syndromes admitted to Italian intensive cardiac care units: a Blitz-3 Registry sub-analysis. J Cardiovasc Med (Hagerstown). 2012;13(3):165-74.	No evidence of cardiac clinical network
Cequier A, Ariza-Sole A, Elola FJ, Fernandez-Perez C, Bernal JL, Segura JV, et al. Impact on Mortality of Different Network Systems in the Treatment of ST-segment Elevation Acute Myocardial Infarction. The Spanish Experience. Rev Esp Cardiol (Engl Ed). 2017;70(3):155-61.	Inadequate information
Chen X, Li M, Jiang H, Li Y, Mo J, Lin P, et al. STEMI Outcomes in Guangzhou and Hong Kong: Two-Centre Retrospective Interregional Study. PLoS One. 2016;11(3):e0149981.	No evidence of cardiac clinical network
Claeys MJ, Dubois P, Boland J, De Raedt H, Coussement P, Vranckx P, et al. Impact of transition of thrombolysis to primary PCI on door-to-balloon time and on mortality. A population study of STEMI patients in Belgium. Eur Heart J. 2013;34:330-1.	Conference abstract
Claeys MJ, Sinnaeve PR, Convens C, Dubois P, Pourbaix S, Vranckx P, et al. Quality assessment in Belgian ST elevation myocardial infarction patients: results from the Belgian STEMI database. Acta Cardiol. 2018;73(6):529-33.	Inadequate information
Corrada E, Mennuni MG, Grieco N, Sesana G, Beretta G, Presbitero P. Neurological recovery after out-of-hospital cardiac arrest: hospital admission predictors and one-year survival in an urban cardiac network experience. Minerva Cardioangiol. 2013;61(4):451-60.	Full text unobtainable
Courtiol G, Debax P, Lamboley L, Pili P, Deschanel G, Latappy M, et al. Treatment of acute cardiac failure in the emergency department. Improve our practices? Data from the RESURCOR network. Archives of Cardiovascular Diseases Supplements. 2016;8(1):31.	Conference abstract
Curran HJ, Hubacek J, Southern D, Galbraith D, Knudtson ML, Ghali WA, et al. The effect of a regional care model on cardiac catheterization rates in patients with Acute Coronary Syndromes. BMC Health Serv Res. 2014;14:550.	No evidence of cardiac clinical network
Danchin N, Coste P, Ferrieres J, Steg PG, Cottin Y, Blanchard D, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the french registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation. 2008;118(3):268-76.	No evidence of cardiac clinical network
Dansky K, Vasey J. Managing heart failure patients after formal homecare. Telemed J E Health. 2009;15(10):983-91.	No evidence of cardiac clinical network
Dansky KH, Vasey J, Bowles K. Use of telehealth by older adults to manage heart failure. 2008;1(1):25-32.	No evidence of cardiac clinical network
Dansky KH, Vasey J, Bowles K. Impact of telehealth on clinical outcomes in patients with heart failure. Clin Nurs Res. 2008;17(3):182-99.	No evidence of cardiac clinical network
De Antonio M, Domingo M, Diez-Lopez C, Gonzalez B, Cabanes R, Rodriguez M, et al. Impact of an organized regional primary PCI network on heart failure patient characteristics in a heart failure clinic: 2001-2008 vs. 2009-2015. Eur Heart J. 2016;37:533.	Conference abstract
De Gennaro L, Donadeo V, Bulzis G, Ricci G, Citarelli G, Resta M, et al. Telemonitoring and teleconsultation in the management of patients with chronic heart failure or chronic obstructive pulmonary disease (progetto Telescopico). Eur J Heart Fail. 2016;18:85.	Conference abstract
De Luca L, Saia F. Evolution of STEMI network in Italy. Minerva Cardioangiol. 2018;66(4):392-9.	Full text unobtainable

Study	Reason for exclusion
De Maria E, Ricci S, Cappelli S, Benenati PM, Patrizi G. Feasibility of transradial approach in a hub and spoke cath lab network. Minerva Cardioangiol. 2010;58(1):11-5.	Full text unobtainable
De Maria R, Mortara A, Battistoni I, Iacoviello M, Navazio A, Pini D, et al. The Italian heart failure care network guidance document. Eur J Heart Fail. 2016;18:95.	Conference abstract
Di Pasquale G, Riva L, De Palma R, Guastaroba P, Berti E, Pavesi PC, et al. Performance indicators in a large Italian STEMI network. Cardiology (Switzerland). 2013;126:9.	Conference abstract
Djambazov S, Zhivkov A, Maznev I, Ingeliev M, Slavov R, Cvetkova N, et al. Setting up a successful network for primary PCI treatment: 2 years' experience. European Heart Journal, Supplement. 2010;12:F74.	Conference abstract
Doolin B, Hamer AW. Network-based transformation of cardiac care in New Zealand. 2014:69-100.	No evidence of cardiac clinical network
El Khoury C, Serre P, Flocard E, Capel O, Jacob X, Banaei L, et al. A well organized regional network is a major determinant of improvement of acute myocardial infarction management. Eur Heart J. 2011;32:869.	Conference abstract
Ertl G, Angermann CE, Bekeredjian R, Beyersdorf F, Güder G, Gummert J, et al. Structure and organization of heart failure networks (HF-NETs) and heart failure units (HFUs) to optimize treatment of acute and chronic heart failure: Joint recommendations of the DGK and the DGTHG for the treatment of heart failure. Kardiologe. 2016;10(4):222-35.	No evidence of cardiac clinical network
Evers JM. The Efficacy of STEMI Networks and Systems of Coordinated STEMI Care: An Evaluation of the Implementation of a STEMI Network. 2015.	No evidence of cardiac clinical network
Faupel A, Fraunhofer H, Barth M, Galland A, Mang S, Streicher A, et al. Door to balloon time less than 30 minutes telemetry of 12 canal ecg in the prehospital phase of acute STEMI results for the period of 7 years from 2007 until 2013 including 1050 patients. Eur Heart J. 2014;35:1039.	Conference abstract
Fernández-Rodríguez D, Regueiro A, Freixa X, Trilla M, Masotti M. Persistence of 'gender gap' in St-segment elevation myocardial infarction networks. Circulation. 2015;132.	Conference abstract
Filgueiras Filho NM, Solla DJ, Argolo FC, Braghiroli OF, Paiva-Filho IM, Lima MB, et al. Implementing a regionalized integrated network for st-segment-elevation myocardial infarction (STEMI) care is associated with higher use of evidence-based medication and better survival among STEMI patients: Long-term results from the resisst registry. Circulation. 2015;132.	Conference abstract
Floris R, Sori P, Boscarelli D, Contu P, Iasiello G, Pinna G, et al. Performance of a standardized network for stemi patients initially evaluated by the emergency medical service in an urban area. G Ital Cardiol. 2011;12(12):e243.	Conference abstract
Fordyce CB, Al-Khalidi HR, Jollis JG, Roettig ML, Bagai A, Berger PB, et al. Specific care process implementation associated with improved reperfusion times across multiple STEMI networks: Insights from the AHA mission: Lifeline STEMI accelerator program. Circulation. 2015;132.	Conference abstract
Fordyce CB, Ramanathan K, Park JE, Vandegriend RA, Cairns JA, Perry M, et al. Evolution of a regional stemi reperfusion model: The 6-year vancouver coastal health authority experience. Canadian Journal of Cardiology. 2014;30(10):S116.	Conference abstract
Fordyce CB, Ramanathan K, Pu A, Imrie J, Orenstein T, Perry M, et al. Impact of pre-hospital electrocardiograms and mode of patient presentation on in-hospital mortality in a regional model of ST-elevation myocardial infarction care. Circulation. 2011;124(21).	Conference abstract
Forsyth CJ, Pathak EB, Strom JA. De Facto regionalization of care for ST-elevation myocardial infarction in Florida, 2001-2009. Am Heart J. 2012;164(5):681-8.	No evidence of cardiac clinical network
Fosbol EL, Granger C, Jollis J, Monk L, Lin L, Lytle B, et al. The impact of an emergency medical services hospital bypass protocol on reperfusion time for patients	Conference abstract

Study	Reason for exclusion
with ST-Elevation myocardial infarction (STEMI). Circulation: Cardiovascular Quality and Outcomes. 2012;5(3).	
Fosbol EL, Granger CB, Jollis JG, Monk L, Lin L, Lytle BL, et al. The impact of a statewide pre-hospital STEMI strategy to bypass hospitals without percutaneous coronary intervention capability on treatment times. Circulation. 2013;127(5):604-12.	Inadequate information
Garro N. Hospital network with immediate retransfer of low-risk patients following primary PCI: Eureka (in Service Urgent Revascularisation for STEMI patients coming from spoKe health cAre centres) registry. EuroIntervention. 2014.	Conference abstract
Garza M. Priority traffic. STEMI networks perform: Southern California consortium cuts door-to-balloon times. JEMS: Journal of Emergency Medical Services. 2008;33(2):22-3.	Conference abstract
Gehani AA, Al Suwaidi JM, Tamimi O, Arabi AR, Al Qahtani A, Arafa SO, et al. Pre-hospital trans-satellite wireless 12 lead ECG transmission from the ambulance to primary PCI centre. Eur Heart J. 2015;36:688.	Conference abstract
Germinal F, Alemanni E, Calogiuri R, De Vitis V, Greco G, Mastrolia D, et al. Early nursing transfer after primary-PCI: The Salento model. EuroIntervention. 2015.	Conference abstract
Geyer B, Vadeboncoeur T, Sanders AB, Buttram S, Clark L, Spaite D, et al. Bypassing out-of-hospital cardiac arrest patients to specialty centers results in improved survival. Academic Emergency Medicine. 2010;17:S143.	Conference abstract
Giuliano Ide C, Barcellos Junior CL, von Wangenheim A, Coutinho MS. Issuing electrocardiographic reports remotely: experience of the telemedicine network of Santa Catarina. Arq Bras Cardiol. 2012;99(5):1023-30.	Not in a high development index or EU country
Gogo P, Watkins M, Terrien E, El-Gharib N, Dauerman H. A bivalirudin-switching strategy for a regional transfer system for primary ST-segment myocardial infarction percutaneous coronary intervention. EuroIntervention. 2010;6.	Conference abstract
Gomes V, Trigo J, Gago P, Mimoso J, Faria R, Marques N, et al. A pre-hospital emergency system 'Green Way AMI' improves heart failure rate at 6 months in STEMI patients. European Journal of Heart Failure, Supplement. 2009;8:ii561.	Conference abstract
Guirgis M, Kumar K, Zieroth S, Philipp R, Menkis AH, Freed DH. Interprovincial spoke-to-hub transport using the Impella Recover LP 5.0 left ventricular assist device as a bridge to long-term circulatory support. Can J Cardiol. 2010;26(8):320-2.	No evidence of cardiac clinical network
Gustafsson I, Madsen LH, Gustafsson F, Schou M, Videbaek L, Hildebrandt PR. Optimal treatment in specialized heart failure clinics does not prevent poor outcome in diabetic patients with chronic heart failure. An analysis from the Danish Heart Failure Clinics Network. European Journal of Heart Failure, Supplement. 2009;8:ii547.	Conference abstract
Hansen CM, Wissenberg M, Weeke P, Zinckernagel L, Ruwald MH, Karlsson L, et al. Danish AED network with linkage to emergency medical services covered more than half of public cardiac arrests in high-incidence areas. Resuscitation. 2013;84:S64-S5.	Conference abstract
Harjai KJ, Orshaw P, Yaeger L, Ruda J, Ellis G, Health G. A Novel reperfusion strategy for STEMI patients presenting to non-PCI hospitals in a rural STEMI network. Crit Pathw Cardiol. 2011;10(3):158.	Conference abstract
Harjai KJ, Orshaw P, Yaeger L, Ellis G, Kirtane A. Variability in maximal suggested door-in-door-out time for hospitals transferring patients for primary angioplasty in STEMI. J Interv Cardiol. 2013;26(6):596-603.	Inadequate information
Heitzler VN, Babic Z, Milicic D, Bergovec M, Raguz M, Mirat J, et al. Primary percutaneous coronary interventio network in economically less developed country. European Heart Journal, Supplement. 2010;12:F106.	Conference abstract
Hernández-Quiles C, Garcia-Serrano R, Bernabeu-Witte M, Ruiz-Cantero A, Colmenero-Camacho M-A, Ollero-Baturone M. A randomized clinical trial for remote telemonitoring into an integrated care program for high complexity patients. Atlan-TIC project. International Journal of Integrated Care (IJIC). 2016;16(6):1-2.	Conference abstract
Hinton S, Geukers K, Heckman G, Suskin N, Hartley T, Harkness K, et al. The 'hub and spoke' model of heart function care achieves quality index markers. Circulation.	Conference abstract

Study	Reason for exclusion
2018;137.	
Hsia RY, Sabbagh S, Sarkar N, Sporer K, Rokos IC, Brown JF, et al. Trends in Regionalization of Care for ST-Segment Elevation Myocardial Infarction. Western Journal of Emergency Medicine: Integrating Emergency Care with Population Health. 2017;18(6):1010-7.	Inadequate information
Huang WC, Kuo FY, Mar GY, Chiou KR, Cheng CC, Lin SL, et al. The effect of continous quality improvement method on reducing door-to-balloon time and mortality in patients with st-segment elevation acute myocardial infarction. EuroIntervention. 2010;6.	Conference abstract
Huitema AA, Harkness K, Heckman GA, McKelvie RS. The Spoke-Hub-and-Node Model of Integrated Heart Failure Care. Can J Cardiol. 2018;34(7):863-70.	Review
Incani A, Poon K, Dahl M, Fu J, Muller H, Dooris M, et al. Does the presence of ongoing chest pain influence triage and transfer in an acute coronary syndrome network? Heart Lung and Circulation. 2011;20:S204.	Conference abstract
Incani A, Poon K, Dahl M, Fu J, Muller H, Dooris M, et al. The demographic profile of patients with acute coronary syndromes referred for invasive treatment in a large clinical network using a novel web-based triage and transfer system. Heart Lung and Circulation. 2011;20:S43.	Conference abstract
Izzo A, Mantovani P, Tomasi L, Dall'oglio L, Bonatti S, Rosiello R, et al. Reduction of general mortality in a coronary care unit of a cure network for acute myocardial infarction. European Heart Journal, Supplement. 2010;12:F4.	Conference abstract
Jackevicius CA, de Leon NK, Lu L, Chang DS, Warner AL, Mody FV. Impact of a Multidisciplinary Heart Failure Post-hospitalization Program on Heart Failure Readmission Rates. Annals of Pharmacotherapy. 2015;49(11):1189-96.	No evidence of cardiac clinical network
Jacobshagen C, Kern M, Scholz KH, Hasenfuss G, Maier LS. Reducing contact-to-balloon-time by increasing the number of primary transportations to PCI centers: Results from the myocardial infarction network Goettingen. Eur Heart J. 2010;31:768.	Conference abstract
Jaeger B, Farhan S, Rohla M, Christ G, Schreiber W, Podczeck-Schweighofer A, et al. Temporal trends from a metropolitan STEMI Registry (2003-2009): Patients characteristics, delay times and long-term mortality. European Heart Journal: Acute Cardiovascular Care. 2015;4:316.	Conference abstract
Jaeger B, Lanschuetzer L, Sebald D, Kaff A, Huber K. Prehospital delay is affected by daytime and operation site in a metropolitan STEMInetwork. European Heart Journal: Acute Cardiovascular Care. 2016;5:7-8.	Conference abstract
James GJ, Hussein RA-K, Mayme LR, Peter BB, Claire CC, Harold LD, et al. Regional Systems of Care Demonstration Project. Circulation. 2016;134(5):365-74.	Inadequate information
Jangwal H, Parker H, Barger B, Smith K, Toogood G, Soon K, et al. Pre-hospital notification trial for primary PCI: A collaboration between the Victorian cardiac clinical network (department of health), ambulance Victoria and participating Victorian public hospitals. Heart Lung and Circulation. 2012;21:S168-S9.	Conference abstract
Janus B, Rakowski T, Dziewierz A, Fijorek K, Sokolowski A, Dudek D. Effect of introducing a regional 24/7 primary percutaneous coronary intervention service network on treatment outcomes in patients with ST segment elevation myocardial infarction. Kardiol Pol. 2015;73(5):323-30.	No evidence of cardiac clinical network
Johnson BK, Newell MC, Kalra A, Sengupta J, Hauser RG, Katsiyiannis WT, et al. Underutilization of implantable cardioverter-defibrillators in appropriate patients in a regional ST-elevation myocardial infarction system. Circulation. 2013;128(22).	Conference abstract
Jollis JG, Al-Khalidi HR, Roettig ML, Berger PB, Corbett CC, Doerfler SM, et al. Impact of Regionalization of ST-Segment-Elevation Myocardial Infarction Care on Treatment Times and Outcomes for Emergency Medical Services-Transported Patients Presenting to Hospitals With Percutaneous Coronary Intervention: Mission: Lifeline Accelerator-2. Circulation. 2018;137(4):376-87.	No evidence of cardiac clinical network
Jollis JG, Granger CB, Henry TD, Antman EM, Berger PB, Moyer PH, et al. Systems of	No evidence of cardiac

Study	Reason for exclusion
care for ST-segment-elevation myocardial infarction: a report From the American Heart Association's Mission: Lifeline. Circ Cardiovasc Qual Outcomes. 2012;5(4):423-8.	clinical network
Jones DA, Bromage DI, Rathod KS, Lim P, Virdi G, Jain AJ, et al. Impact of inter-hospital transfer for primary percutaneous coronary intervention on survival (10 108 stemi patients from the london heart attack group). Heart. 2013;99:A22-A3.	Conference abstract
Juzar D, Isman F, Suridanda S, Tobing D, Ariwibowo D, Dewayani R, et al. Regionalizing STEMI receiving center within a metropolitan city shorten ischemic time: Data collected from iSTEMI pilot project. European Heart Journal: Acute Cardiovascular Care. 2015;4:290-1.	Conference abstract
Kalra SS, Knott K, Dennis A, Khan F, Firoozi S. Quality comparison of different primary angioplasty activation service models within a single cardiac centre. J Am Coll Cardiol. 2015;66(15):B91.	Conference abstract
Kelly AM, Pannifex J. Improving management of atrial fibrillation across a health system using a clinical network. Eur Heart J. 2014;35:780.	Conference abstract
Kern KB. Usefulness of cardiac arrest centers - extending lifesaving post-resuscitation therapies: the Arizona experience. Circ J. 2015;79(6):1156-63.	No evidence of cardiac clinical network
Kim A, Yoon SJ, Kim YA, Kim EJ. The burden of acute myocardial infarction after a regional cardiovascular center project in Korea. Int J Qual Health Care. 2015;27(5):349-55.	No evidence of cardiac clinical network
Kingsbury KJ, Natarajan MK, Forsey A, Oakes GH, Bakar-Irwin S. A provincial approach to improving stemi care in Ontario. Canadian Journal of Cardiology. 2014;30(10):S81.	Conference abstract
Kleczynski P, Siudak Z, Dziewierz A, Tokarek T, Rakowski T, Legutko J, et al. The network of invasive cardiology facilities in Poland in 2016 (data from the ORPKI Polish National Registry). Kardiol Pol. 2018;76(4):805-7.	Editorial or Commentary
Korczyk D, McPherson B, Hickey A, Peters R, Cook C. Telemedicine in heart failure: Heart failure service support for south west Queensland. European Journal of Heart Failure, Supplement. 2010;9:S221.	Conference abstract
Kozinski M, Pstragowski K, Kubica JM, Fabiszak T, Kasprzak M, Kuffel B, et al. ACS network-based implementation of therapeutic hypothermia for the treatment of comatose out-of-hospital cardiac arrest survivors improves clinical outcomes: the first European experience. Scand J Trauma Resusc Emerg Med. 2013;21:22.	No evidence of cardiac clinical network
KPLC News. STEMI Network activated for rural cardiac patients. 2013.	Unreliable source
Kuijt WJ, Koch KT, Haeck JD, Verouden NJ, Henriques JP, Baan J, et al. Direct presentation, field-referral, and interhospital transfer in a network-based system for primary percutaneous coronary intervention for ST-elevation myocardial infarction result in similar 1-year mortality. J Am Coll Cardiol. 2009;53(10):A57.	Conference abstract
Kuo FY, Huang WC, Mar GY, Cheng CC, Tsai HL, Chiou KR, et al. The effect of failure mode and effect analysis on reducing door-to-balloon time and mortality in ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2009;53(10):A329.	Not in a high development index or EU country
LaBarbera M, Shaw R, Brewster J, Pang D, Coleman P, Greene R, et al. Treatment and outcomes of 2580 patients with unprotected left main coronary artery disease in a real-world hospital network: A five year experience (2005-2009). Catheterization and Cardiovascular Interventions. 2011;77:S73-S4.	Conference abstract
Lambert LJ, Clément L, Boothroyd LJ, Beauchamp C, Carroll C, Bogaty P. Time-critical cardiovascular care in Québec: Advantages of a novel collaborative initiative to improve outcomes for both acute myocardial infarction and ischemic stroke. Canadian Journal of Cardiology. 2013;29(10):S258.	Conference abstract
Lanschuetzer L, Jaeger B, Sebald D, Kaff A, Huber K. Public campaign is associated with longterm shortening of pre-hospital delay in a metropolitan STEMI network. European Heart Journal: Acute Cardiovascular Care. 2016;5:10.	Conference abstract
Laprérie AL, Trochu JN. Current perspectives for therapeutic education and health	Inadequate information

Study	Reason for exclusion
management networks. Thoughts based on the French Respecticoeur network's experience. Medecine des Maladies Metaboliques. 2013;7(2):149-54.	
Lauck S, Galte C, Barr S, McGladrey J, Rinzema S. Optimizing care and improving access: Development and implementation of a provincial model for atrial fibrillation clinics. Canadian Journal of Cardiology. 2010;26:163D.	Conference abstract
Lawson WE, Wilbert L, Sokoloff L, Srinivas G, Viccellio P, Dowdy E, et al. Continuing to improve the D2B process. Circulation: Cardiovascular Quality and Outcomes. 2014;7.	Conference abstract
Le May M, Cantor W, Natarajan M, Purdham D, Brezinov M, Kingsbury K, et al. Door-to-balloon time as a function of mode of referral: Results from the ontario provincial cardiac care network database. J Am Coll Cardiol. 2012;60:B141.	Conference abstract
Lian D, Oakes GH, Kingsbury KJ. Geographic analysis of primary PCI access in Ontario: Service areas and population coverage of Ontario Pci Centres. Canadian Journal of Cardiology. 2015;31(10):S2.	Conference abstract
Lidon RM, Baneras J, Barrabes JA, Garcia Del Blanco B, Otaegui I, Garcia-Dorado D. The first ST elevation myocardial infarction in diabetic patients: Characteristics, delays and morbi-mortality within an established network for reperfusion therapy. Eur Heart J. 2014;35:656.	Conference abstract
Liem SS, van der Hoeven BL, Schalij MJ, van der Wall EE. Optimalisation of preclinical, clinical and chronic care for patients with acute MI: MISSION! possible. Neth Heart J. 2005;13(1):1-3.	Editorial or Commentary
Lima B, Manos JA, Duncan M, Noesges SM, Anonetapipat W, Stockard E, et al. Overview of a newly developed hub and spoke extracorporeal membrane oxygenation inter-hospital transport program. Journal of Heart and Lung Transplantation. 2015;34(4):S206.	Conference abstract
Lindholm D, Hlatky MA, James S, Lagerqvist B, Varenhorst C. A method to assess the effect of driving distance to hospital care. Eur Heart J. 2017;38:589.	No evidence of cardiac clinical network
Luers C, Edelmann F, Wachter R, Pieske B, Mende M, Angermann C, et al. Prognostic impact of diastolic dysfunction in patients with heart failure with reduced ejection fraction: A cross-sectional analysis from the German Competence Network Heart Failure. Eur Heart J. 2014;35:1036.	Research networks, Information Networks, Communities of Practice, or Studies that utilised clinical networks to obtain samples for their study
Lupi L, Glisenti F, Castiello A, Visco E, Papa I, Dinatolo E, et al. A telemonitoring program for primary and secondary prevention of cardiovascular disease. Eur Heart J. 2017;38:855.	Conference abstract
Magnavacchi P, Paganelli C, Cappelli C, Tondi S. Primary pci for stemi in a hub and spoke network model: Can a selected reperfusion strategy improve short and long-term outcome? G Ital Cardiol. 2012;13(5):5S-6S.	Conference abstract
Magnavacchi P, Paganelli C, Tondi S, Cappelli C. Long-term clinical outcome of primary pci versus fibrinolysis for st-elevation myocardial infarction: Results from a single center prospective registry. G Ital Cardiol. 2012;13(5):164S-5S.	Conference abstract
Malik AO, Abela O, Allenback G, Devabhaktuni S, Lui C, Singh A, et al. ST-segment elevation myocardial infarction, systems of care. An urgent need for policies to co-ordinate care in order to decrease in-hospital mortality. Int J Cardiol. 2017;240:82-6.	No evidence of cardiac clinical network
Man J, Edwards R. Primary percutaneous coronary Intervention vs pre-hospital thrombolysis for acute myocardial infarction in patients in rural Northumberland, United Kingdom. Eur Heart J. 2010;31:496.	Conference abstract
Mariani J, de Abreu M, Tajer CD. Time to and use of reperfusion therapy in a health care network. Revista Argentina de Cardiologia. 2013;81(3):233-9.	Not in a high development index or EU country
Marzegalli M, Fontana G, Sesana G, Grieco N, Lombardi F, Elena C, et al.	Full text unobtainable

Study	Reason for exclusion
[Cardiological emergency network in Lombardy]. G Ital Cardiol (Rome). 2008;9(10 Suppl 1):56s-62s.	
McAlister FA, Bakal JA, Kaul P, Quan H, Blackadar R, Johnstone D, et al. Changes in heart failure outcomes after a province-wide change in health service provision a natural experiment in Alberta, Canada. Circ Heart Fail. 2013;6(1):76-82.	No evidence of cardiac clinical network
McLean S, Egan G, Connor P, Flapan AD. Collaborative decision-making between paramedics and CCU nurses based on 12-lead ECG telemetry expedites the delivery of thrombolysis in ST elevation myocardial infarction. Emergency Medicine Journal. 2008;25(6):370-4.	No evidence of cardiac clinical network
McLenachan JM, Gray HH, de Belder MA, Ludman PF, Cunningham D, Birkhead J. Developing primary PCI as a national reperfusion strategy for patients with ST-elevation myocardial infarction: the UK experience. EuroIntervention. 2012;8 Suppl P:P99-107.	Inadequate information
Montisci R, Floris R, Cadeddu M, Decandia GF, Lai G, Pirisi R, et al. The difficult task of reducing symptom-onset-to-balloon time among patients undergoing primary PCI. Eur Heart J. 2015;36:74.	Conference abstract
Montisci R, Ruscazio M, Floris R, Marchetti MF, Cacace C, Scano F, et al. Impact of an emergency network for STEMI in patients with different age. J Am Coll Cardiol. 2015;65(10):A97.	Conference abstract
Moraes PIM, Peternelli DG, Nunes AR, Santos EVS, Reggi S, Sousa JMA, et al. Pharmaco invasive strategy for ST elevation myocardial infarction (STEMI) is able to significantly reduce mortality with a low NNT in a very populated city. Eur Heart J. 2015;36:747.	Conference abstract
Morrison LJ, Dorian P, Dainty KN, Brooks S, Thorpe K, Zhan C, et al. Employing knowledge translation interventions to increase the use of therapeutic hypothermia post arrest: The SPARC Network Trial. Critical Care. 2011;15:S110.	Conference abstract
Morrison LJ, Dorian P, Dainty KN, Brooks SC, Thorpe K, Zhan C, et al. Survival after post-arrest therapeutic hypothermia: Secondary analysis of the strategies for post-arrest care (SPARC) stepped-wedge trial. Circulation. 2011;124(21).	Conference abstract
Morrison LJ, Rac VE, Dorian P, Cheskes S, Fowler R, Dainty KN, et al. Gender differences in access to post-arrest care: A SPARC network cohort study. Canadian Journal of Emergency Medicine. 2014;16:S28.	Conference abstract
Muraglia S, Tedoldi F, Zilio F, Menotti A, Dallago M, Braito G, et al. The network for the invasive management of the out of hospital cardiac arrest: A regional experience. G Ital Cardiol. 2016;17(10):e51.	Conference abstract
Murdoch D, Gibbs H, Blenkhorn A, Mumford D, Kwan P. A new cardiac catheterisation laboratory in northern NSW: Experiences of the first year. Heart Lung and Circulation. 2011;20:S22.	Conference abstract
Natarajan D, Soon K, Cox N, Adel A, Marasovic S, Zakariyya A, et al. Ambulance pre-notification of stemi markedly reduces door-to-first device time-single centre's preliminary results. Heart Lung and Circulation. 2012;21:S145.	Conference abstract
Natarajan MK, Forsey A, Wijeysundera HC, Oakes G, Cantor WJ, Kassam SA, et al. Trends in PCI for patients with ST-segment elevation myocardial infarction at Ontario cardiac centres with and without on-site cardiac surgery. Canadian Journal of Cardiology. 2014;30(10):S67.	Conference abstract
Natarajan MK, Welsford M, Schwalm JD, Knox S, Jolly SS, Mehta SR, et al. Providing a platform for organized care in st elevation myocardial infarction: The LHIN-4 smartami project in Southern Ontario experience. Canadian Journal of Cardiology. 2012;28(5):S259-S60.	Conference abstract
Nazir A, Dennis ME, Unroe KT. Implementation of a heart failure quality initiative in a skilled nursing facility: lessons learned. J Gerontol Nurs. 2015;41(5):26-33.	No evidence of cardiac clinical network
New G, Jangwal H, Parker H, Roberts L, Barger B, Smith K, et al. Pre-hospital notification of STEMI (PNS): Collaboration between the victorian cardiac clinical	Conference abstract

Study	Reason for exclusion
network, ambulance victoria and participating hospitals. J Am Coll Cardiol. 2013;61(10):E120.	
Nguyen V, Owen K, Nguyen P, Juergens C, French J, Lo S, et al. Same day return transfer of lowrisk patients following PCI to improve service access- A safety study. Heart Lung and Circulation. 2011;20:S146.	Conference abstract
Networks NHSLC. Atrial Fibrillation (AF) toolkit: Detect, Protect and Perfect. London, UK: NHS England, 2017.	No evidence of cardiac clinical network
Networks NHSLC. London Clinical Networks in focus 2017-2018. London, UK: NHS, 2018.	Inadequate information
Network NHSSWSC. Bigger, Better, Faster? An options appraisal for the reconfiguration of emergency heart attack and stroke services for the South West of England. England: NHS England, 2016.	No evidence of cardiac clinical network
Nolan JP, Lyon RM, Sasson C, Rossetti AO, Lansky AJ, Fox KA, et al. Advances in the hospital management of patients following an out of hospital cardiac arrest. Heart. 2012;98(16):1201-6.	No evidence of cardiac clinical network
Oakes GH, Forsey A, Velianou JL, Marquis J, Kingsbury KJ. Variability in the rates of normal diagnostic coronary catheterizations and non-invasive pre-catheterization functional testing at advanced cardiac centres in Ontario. Canadian Journal of Cardiology. 2014;30(10):S84.	Conference abstract
Oakes G, Woodward G, Kingsbury K. A quality improvement project to address variability in the rates of normal diagnostic coronary catheterizations and non-invasive pre-catheterization cardiac diagnostic testing in Ontario. 2016. p. S268-S9.	Conference abstract
Ochiai R, Yao A, Kinugawa K, Nagai R, Shiraishi I, Niwa K. Status and future needs of regional adult congenital heart disease centers in Japan. Circ J. 2011;75(9):2220-7.	No evidence of cardiac clinical network
O'Donohue P, Dahl M, Colburn D, Rashford S, Cardwell R, George T, et al. The sunshine coast STEMI pilot: An integrated network model for immediate transfer of regional patientS to a PCI-capable hospital. Heart Lung and Circulation. 2011;20:S150.	Conference abstract
Ono M, Kyo S, Nishimura T, Hisagi M, Nawata K, Kinoshita O. How do we construct an ideal infrastructure for increasing demand of implantable ventricular assist device? J Card Fail. 2010;16(9):S144.	Conference abstract
Paradossi U, Palmieri U, Ravani M, Vaghetti M, Trianni G, Rizza A, et al. Reducing door-to-balloon time in patients with ST-segment elevation myocardial infarction affect in-hospital and one-year mortality: A network experience in Italy. Eur Heart J. 2013;34:78.	Conference abstract
Park JJ, Yoon CH, Suh JW, Cho YS, Youn TJ, Chae IH, et al. Reduction of ischemic time for transferred ST-elevation myocardial infarction patients using a smartphone social network system: 1-year experience. Eur Heart J. 2016;37:1174.	Conference abstract
Patel VK, Vasaiwala S, Vidovich M, Shroff A, Kao J. Regionalized care with STEMI Centers decreases mortality and improves door to balloon times. J Am Coll Cardiol. 2009;53(10):A51.	Conference abstract
Pathak EB, Forsyth CJ, Anic G, Tanner JP, Comins MM, Strom JA. Transfer travel times for primary percutaneous coronary intervention from low-volume and non-percutaneous coronary intervention-capable hospitals to high-volume centers in Florida. Ann Emerg Med. 2011;58(3):257-66.	No evidence of cardiac clinical network
Patterson T, Perkins GD, Joseph J, Wilson K, Van Dyck L, Robertson S, et al. A randomised trial of expedited transfer to a cardiac arrest centre for non-ste out-of hospital cardiac arrest: Arrest. Heart. 2018;104:A7-A8.	Conference abstract
Pearson DA, Heffner A, Gabbard E, Garvey L, Wares C, Karvetski C, et al. Impact of a standardized post-arrest clinical pathway and quality improvement tool on three	Conference abstract

Study	Reason for exclusion
receiving cardiac resuscitation centers within a single healthcare system. Academic Emergency Medicine. 2016;23:S250-S1.	
Pearson DA, Heffner A, Wares C, Garvey L, Karvetski C, Runyon M. Variability of outcomes among three receiving cardiac resuscitation centers within a single health care system. Academic Emergency Medicine. 2015;22(5):S304.	Conference abstract
Peiro Ibanez OM, Sanz E, Bonet G, Serrano I, Rodriguez J, Gonzalez M, et al. Evolution of clinical characteristics and procedures in patients admitted to a coronary care unit: Impact of a STEMI network. European Heart Journal: Acute Cardiovascular Care. 2018;7(1):208-9.	Conference abstract
Pereira H, Cale R, Ferreira RC, Silva JC, Marques J, Ribeiro VG, et al. Networks: What are the immediate consequences of merging centers? Eur Heart J. 2016;37:1066.	Conference abstract
Pereira H, Calé R, Pereira E, Vitorino S, Caldeira D, Mello S, et al. Predictors of system-delay in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. EuroIntervention. 2015.	Conference abstract
Perera D, Hoonjan B, Krishnathasan K, Selvanyagam M, Neugebauer H. Efficacy of the novel heart attack centre extension pathway: A pilot study. Critical Care. 2012;16:S65.	Conference abstract
Perrins CJ, Hunter A, McLachlan C, Assareh H, Ruchin P, McCready M, et al. The safety of remote PCI in 1,543 patients in rural New South Wales without cardiac surgery onsite. Global Heart. 2014;9(1):e290.	Conference abstract
Politi A, Martinoni A, Klugmann S, Zanini R, Onofri M, Guagliumi G, et al. LombardIMA: a regional registry for coronary angioplasty in ST-elevation myocardial infarction. J Cardiovasc Med (Hagerstown). 2011;12(1):43-50.	Full text unobtainable
Posnenkova OM, Duplyakov DV, Kiselev AR, Khokhlunov SM. The results of regional STEMI network: Does in-hospital mortality reflect the effect in clinical practice? European Heart Journal: Acute Cardiovascular Care. 2015;4:124.	Conference abstract
Post F, Giannitsis E, Riemer T, Maier LS, Schmitt C, Schumacher B, et al. Pre- and early in-hospital procedures in patients with acute coronary syndromes: first results of the 'German chest pain unit registry'. Clin Res Cardiol. 2012;101(12):983-91.	No evidence of cardiac clinical network
Radovanovic D, Urban P, Simon R, Schmidli M, Maggiorini M, Rickli H, et al. Outcome of patients with acute coronary syndrome in hospitals of different sizes. A report from the AMIS Plus Registry. Swiss Med Wkly. 2010;140(21-22):314-22.	No evidence of cardiac clinical network
Rakowski T, Dziewierz A, Siudak Z, Kleczynski P, Dubiel JS, Dudek D. Introduction of new oral antiplatelet drugs in myocardial infarction hospital network: initial experience. J Thromb Thrombolysis. 2014;37(3):243-5.	No evidence of cardiac clinical network
Rata M, Cassan S, Mester P, Ispas A, Madiot H, Broin P, et al. Transfer of acute coronary syndrome patients in the Alps (SCAAlpes). Data from the RESURCOR network. Archives of Cardiovascular Diseases Supplements. 2016;8(1):1.	Conference abstract
Rathod KS, Jones DA, Gallagher SM, Bromage DI, Whitbread M, Archbold AR, et al. Out-of-hours primary percutaneous coronary intervention for ST-elevation myocardial infarction is not associated with excess mortality: a study of 3347 patients treated in an integrated cardiac network. BMJ Open. 2013;3(6):e003063.	Not current practice
Rathod KS, Kognati S, Jain A, Knight C, Mathur A, Sirker A, et al. Complete revascularisation versus culprit only lesion intervention in ACS patients with multi-vessel disease: Incidence and outcomes from the London Heart Attack Group. European Heart Journal: Acute Cardiovascular Care. 2018;7(1):157-8.	Conference abstract
Rathod KS, Kognati S, Jain A, Knight C, Mathur A, Sirker A, et al. Culprit lesion versus multi-vessel intervention in patients with cardiogenic shock complicating myocardial infarction: Incidence and outcomes from the London Heart Attack Group. European Heart Journal: Acute Cardiovascular Care. 2018;7(1):143.	Conference abstract
Rathod KS, Jain A, Mathur A, Wragg A, Jones DA. Interhospital Transfer for Primary	Conference abstract

Study	Reason for exclusion
Percutaneous Coronary Intervention Has Worse Outcome Compared With Direct Admission to a Heart Attack Centre: An Observational Study of 25,315 Patients With St-Elevation Myocardial Infarction From the London Heart Attack Group. JACC: Cardiovascular Interventions. 2019;12(4):S6.	
Regueiro-Cueva A, Sabate M, Macaya C, Fernandez-Ortiz A, Goicolea J. STEMI networks and its influence on PCI/primary PCI rates in Spain. European Heart Journal: Acute Cardiovascular Care. 2012;1:18.	Conference abstract
Reimer AP, Hustey FM, Kralovic D. Decreasing door-to-balloon times via a streamlined referral protocol for patients requiring transport. Am J Emerg Med. 2013;31(3):499-503.	Focus is on changes to Emergency Medical Services protocols (e.g. ambulance by-pass protocols) that are not related to cardiac clinical network formation
Ribas Barquet N, Merono Duenas O, Garcia-Garcia C, Fernandez-Gasalla A, Perez BA, Morales Alvares J, et al. In-hospital mortality and long-term prognosis of a reperfusion network STEMI. Analysis of cardiovascular risk factors during follow-up. European Heart Journal: Acute Cardiovascular Care. 2014;3(2):139-40.	Conference abstract
Riva V, Grieco NB, Sorlini C, Ravasi S, Sesana G. Cost-effectiveness of extracorporeal life support networks in refractory out of hospital cardiac arrest. European Heart Journal: Acute Cardiovascular Care. 2016;5:152.	Conference abstract
Rushworth GF, Bloe C, Diack HL, Reilly R, Murray C, Stewart D, et al. Pre-hospital ECG E-transmission for patients with suspected myocardial infarction in the highlands of Scotland. Int J Environ Res Public Health. 2014;11(2):2346-60.	No evidence of cardiac clinical network
Russell D, Rosati RJ, Sobolewski S, Marren J, Rosenfeld P. Implementing a Transitional Care Program for High-Risk Heart Failure Patients: Findings from a Community-Based Partnership Between a Certified Home Healthcare Agency and Regional Hospital. Journal for Healthcare Quality. 2011;33(6):17-24.	No evidence of cardiac clinical network
Saar A, Marandi T, Ainla T, Blondal M, Fischer K, Eha J. Impact of national PCI network on prognosis after acute myocardial infarction in Estonia. Eur Heart J. 2015;36:188.	No evidence of cardiac clinical network
Sanchez-Ross MG, Maher JM, Kasper M, Oghlakian G, Patel B, Dhruva VN, et al. Ripple effects of a novel D2B pathway. J Am Coll Cardiol. 2010;55(10):A109.E1013.	Conference abstract
Sanchez-Ross M, Oghlakian G, Maher J, Patel B, Mazza V, Hom D, et al. The STAT-MI (ST-Segment Analysis Using Wireless Technology in Acute Myocardial Infarction) trial improves outcomes. JACC Cardiovasc Interv. 2011;4(2):222-7.	No evidence of cardiac clinical network
Saraf S, Sandler B, Dickinson K, McWilliams E, Lloyd G, Furniss S, et al. Primary percutaneous coronary intervention (PPCI) in 2 district general hospitals in the United Kingdom - A new model of care. Eur J Intern Med. 2011;22:S85.	Conference abstract
Sardi GL, Loh JP, Torguson R, Satler LF, Waksman R. Real-time, two-way interaction during ST-segment elevation myocardial infarction management improves door-to-balloon times. Cardiovasc Revasc Med. 2014;15(5):263-8.	No evidence of cardiac clinical network
Scardovi AB, De Maria R, De Feo S, Petruzzi MA, Camerini A, Cipriani M, et al. The Italian Network for Heart Failure five years after the publication of the Italian 'Consensus conference on the management of heart failure'. Monaldi Archives for Chest Disease - Cardiac Series. 2012;78(1):40-8.	Editorial or Commentary
Schampaert E, L'Allier P, Kouz S, Whittom L, Ross D, Gagné CE, et al. Im Québec: A stemi database-university of Montréal integrated health network quality assurance initiative: Reperfusion delays and in-hospital outcomes over the first 4 years of utilisation. Canadian Journal of Cardiology. 2015;31(10):S10.	Conference abstract

Study	Reason for exclusion
Scholz KH, von Knobelsdorff G, Ahlersmann D, Keating FK, Jung J, Werner GS, et al. [Optimizing systems of care for patients with acute myocardial infarction. STEMI networks, telemetry ECG, and standardized quality improvement with systematic data feedback]. Herz. 2008;33(2):102-9.	No evidence of cardiac clinical network
Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J, et al. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). Eur Heart J. 2012;34(6):432-42.	No evidence of cardiac clinical network
Scorcu G, Meloni L, Pilleri A, Loi B, Pirisi R, Sanna F, et al. [The network for acute coronary syndromes in the metropolitan area of Cagliari (Italy): management of ST-elevation myocardial infarction, reperfusion time, and adherence to guidelines]. G Ital Cardiol (Rome). 2013;14(1):66-75.	Full text unobtainable
Sefrin P, Maier S. Study Group of the Bavarian Heart Attack Network: Preclinical standards in the treatment of heart attack. Notarzt. 2011;27(3):101-4.	Inadequate information
Senni M, Filippi A. [Tailored follow-up for chronic heart failure patients: time for discussion]. G Ital Cardiol (Rome). 2010;11(5 Suppl 2):5s-7s.	Full text unobtainable
Shahid M, Travis J, Binder L, Tipson R, Flint E. Completing an audit loop of cardiac rehabilitation across the english cardiac networks. European Journal of Cardiovascular Prevention and Rehabilitation. 2010;17:S107.	Conference abstract
Silvain J, Vignalou JB, Bellemain-Appaix A, Landivier A, Barthelemy O, Beygui F, et al. Transfer time is not a major determinant of in-hospital mortality in Primary PCI when performed in a well organized urban network. Eur Heart J. 2009;30:924.	Conference abstract
Sinclair E, Murdoch K, Meddings P. Pre-hospital thrombolysis in rural Victoria: Successes and missed opportunities. Heart Lung and Circulation. 2015;24:S161.	Conference abstract
Siudak Z, Birkemeyer R, Rakowski T, Dziewierz A, Janzon M, Skowronek J, et al. Out-of-hospital cardiac arrest in patients treated with primary PCI for STEMI. Long-term follow up data from EUROTRANSFER registry. Eur Heart J. 2010;31:900.	Research networks, Information Networks, Communities of Practice, or Studies that utilised clinical networks to obtain samples for their study
Smith HE. A novel palliative care program for patients with chronic heart failure that decreased readmission rates. J Card Fail. 2014;20(8):S59.	Conference abstract
Sorensen JT, Maeng M. Regional systems-of-care for primary percutaneous coronary intervention in ST-elevation myocardial infarction. Coron Artery Dis. 2015;26(8):713-22.	Review
South W, South West Congenital Heart Disease N. Patient Pathways for Adults. 2019;2019(23 March).	No evidence of cardiac clinical network
Spaite DW, Bobrow BJ, Stolz U, Berg RA, Sanders AB, Kern KB, et al. Statewide regionalization of postarrest care for out-of-hospital cardiac arrest: association with survival and neurologic outcome. Ann Emerg Med. 2014;64(5):496-506.e1.	No evidence of cardiac clinical network
Starmer G, Schrale R. Heart of the tropics: delivering evidence-based care for acute coronary syndromes in northern Australia. Rural & Remote Health. 2016;16(4):1-7.	No evidence of cardiac clinical network
Steffenino G, Chinaglia A, Noussan P, Alciati M, Bongioanni S, Rolfo C, et al. Care of acute myocardial infarction in the coronary care units of Piedmont in 2007: results from the 'PRIMA_sweet' region-wide survey. J Cardiovasc Med (Hagerstown). 2013;14(5):354-63.	Research networks, Information Networks, Communities of Practice, or Studies that utilised clinical networks to obtain samples for their study
Steinberg BA, Jollis JG, Winkler A, Granger C, Newby LK. Treatment pathways and quality improvement for patients with acute myocardial infarction at a tertiary care center. Crit Pathw Cardiol. 2012;11(2):77-80.	No evidence of cardiac clinical network;
Stewart RAH, Somaratne JB. Left ventricular thrombus (LVT) after st elevation	Conference abstract

Study	Reason for exclusion
myocardial infarction (STEMI) in auckland region STEMI network (ARSN) benjamin liu. Heart Lung and Circulation. 2018;27:S22.	
Stub D, Lauck S, Lee M, Gao M, Chan A, Della Siega A, et al. Regional systems of care to optimise outcomes in patients undergoing transcatheter aortic valve implantation (TAVI). Heart Lung and Circulation. 2015;24:S297.	Conference abstract
Takayama M, Takagi A, Miyauchi K, Ito S, Yoshikawa M, Miyachi S, et al. Emergency transport detail of patients with acute myocardial infarction in Tokyo metropolitan area. European Heart Journal: Acute Cardiovascular Care. 2012;1:112-3.	Conference abstract
Tatu-Chitoiu GP, Deleanu D, Arafat R, Zarma L, Calmac L, Macarie C, et al. Primary coronary angioplasty in patients with STtelevation myocardial infarction in the Bucharest (Romania) area. Over the stent for life initiative target one year after the network opening. European Heart Journal: Acute Cardiovascular Care. 2012;1:59.	Conference abstract
Tatu-Chitoiu GP, Deleanu D, Macarie C, Calmac L, Udroiu C, Chioncel O, et al. Impact on the in-hospital mortality of the STEMI regional network around Bucharest, Romania. RO-STEMI registry. European Heart Journal: Acute Cardiovascular Care. 2014;3(2):105-6.	Conference abstract
Tatu-Chitoiu GP, Deleanu D, Petris A, Macarie C, Arsenescu Georgescu C, Petrescu L, et al. A national PCI network and a pharmacoinvasive strategy, keys of success of the Romanian STEMI program. Eur Heart J. 2014;35:545-6.	Conference abstract
Tatu-Chitoiu GP, Deleanu D, Petris A, Macarie C, Petrescu L, Arsenescu Georgescu C, et al. Lower in-hospital mortality in STEMI patients with postponed angioplasty after successful pre-transfer medication compared with primary angioplasty. RO-STEMI registry data. Eur Heart J. 2014;35:310.	Conference abstract
Tedoldi F, Muraglia S, Braito G, Dallago M, Menotti A, Zilio F, et al. Building of a network for the management of out of hospital cardiac arrest: Experience of an italian mountainous region. J Am Coll Cardiol. 2016;68(18):B343-B4.	Conference abstract
Thilo C, Bluthgen A, von Scheidt W. Efficacy and limitations of a STEMI network: 3 years of experience within the myocardial infarction network of the region of Augsburg - HERA. Clin Res Cardiol. 2013;102(12):905-14.	Research networks, Information Networks, Communities of Practice, or Studies that utilised clinical networks to obtain samples for their study
Thomson C, Curtis R. Saint Thomas chest pain network. Crit Pathw Cardiol. 2008;7(3):204.	Conference abstract
Tideman P, Tirimacco R, Simpson P. Cardiac clinical network, reducing total length of stay for AMI patients. Heart Lung and Circulation. 2010;19:S212.	Conference abstract
Tideman P, Tirimacco R, Simpson P, Cowley P, Siew M. Development of an integrated, digitally-based & state-wide cardiac clinical management network. Heart Lung and Circulation. 2013;22:S212.	Conference abstract
Timoteo AT, Ramos R, Toste A, Oliveira JA, Patricio L, Ferreira ML, et al. Influence of pre-hospital direct transportation to a reference center in the results of primary angioplasty. European Heart Journal, Supplement. 2010;12:F6.	Conference abstract
Tirimacco R, Tideman P, Simpson P. Design, implementation, and outcomes for point-of-care pathological testing in a cardiac clinical network. Point Care. 2009;8(2):56-60.	No evidence of cardiac clinical network
Toleva O, Westerhout CM, Senaratne M, Bode C, Lindroos M, Ardissino D, et al. Association of hub and spoke practice patterns with coronary intervention and outcomes in non ST elevation acute coronary syndromes (NSTE ACS): Insights from the early glycoprotein IIb/IIIa inhibition in NSTE ACS (early-ACS) trial. J Am Coll Cardiol. 2011;57(14):E1101.	No evidence of cardiac clinical network
Tomassini F, Gagnor A, Tizzani E, Giolitto S, Giay Pron P, Infantino V, et al. In-hospital and long-term outcomes of patients with STEMI with unprotected left main coronary artery stenosis undergoing primary PCI in a hospital without on-site cardiac	Conference abstract

Study	Reason for exclusion
surgery. EuroIntervention. 2011;7:M62.	
Tubaro M. STEMI systems of care. Cardiology (Switzerland). 2013;126:230.	Full text unobtainable
Tubaro M, Pillon S, Greco C, Cataldi S, Guasticchi G, Gabriele S, et al. Telecardiology and the network ambulances-hospitals: The Lazio region experience of acute coronary syndromes network 2007. Mediterranean Journal of Pacing and Electrophysiology. 2008;10(1-2):45-52.	Conference abstract
Turner GO. A personal perspective: can legislated state regional STEMI centers provide timely STEMI treatment while overlooking early fibrinolysis? Crit Pathw Cardiol. 2013;12(4):184-7.	Editorial or Commentary
Vanderbilt H. STEMI network. Nashville, TN: Vanderbilt Heart, 2011.	Editorial or Commentary
Viswanathan K, Beith C, Pittaway L, Veevers W, Vickers C. An integrated multi-professional approach to AF management: Initial experience and short-term outcomes of a new rapid access clinic in secondary care. Europace. 2018;20:iv54.	Conference abstract
Wakefield BJ, Bylund CL, Holman JE, Ray A, Scherubel M, Kienzle MG, et al. Nurse and patient communication profiles in a home-based telehealth intervention for heart failure management. Patient Educ Couns. 2008;71(2):285-92.	No evidence of cardiac clinical network
Wakefield BJ, Holman JE, Ray A, Scherubel M, Burns TL, Kienzle MG, et al. Outcomes of a home telehealth intervention for patients with heart failure. J Telemed Telecare. 2009;15(1):46-50.	No evidence of cardiac clinical network
Wakefield BJ, Ward MM, Holman JE, Ray A, Scherubel M, Burns TL, et al. Evaluation of home telehealth following hospitalization for heart failure: a randomized trial. Telemed J E Health. 2008;14(8):753-61.	No evidence of cardiac clinical network
Williams H, Hughes R, Simkins L, Hatton K, Currie M, Chong H, et al. South East London Cardiac Prescribing Forum: working to improve clopidogrel prescribing across the South East London sector. British Journal of Cardiology. 2008;15(6):307-11.	No evidence of cardiac clinical network
Williams H. Influencing cardiovascular prescribing across a managed clinical network. Clinical Pharmacist. 2010;2(9):S2-S3.	Conference abstract
Wong GC, Perry MJ, Ramanathan K. Reduction in door to balloon times after regionalization of inter-facility transfer for primary PCI: The vancouver coastal health authority experience. Canadian Journal of Cardiology. 2012;28(5):S189.	Conference abstract
Wong JM, Fitton C, Anwar S, Stacey S. Intensive care implications of merging heart attack centre units in London. Critical Care. 2016;20.	Conference abstract
Woodend AK, Sherrard H, Fraser M, Stuewe L, Cheung T, Struthers C. Telehome monitoring in patients with cardiac disease who are at high risk of readmission. Heart Lung. 2008;37(1):36-45.	No evidence of cardiac clinical network
Zanini R, Buffoli F, Tomasi L, Izzo A, Lettieri C, Cicorella N, et al. Systematic quality control for management of ST elevation acute myocardial infarction in setting of local network. Minerva Cardioangiol. 2010;58(2):183-92.	Full text unobtainable
Zeymer U, Arntz HR, Dirks B, Ellinger K, Genzwurker H, Nibbe L, et al. Reperfusion rate and inhospital mortality of patients with ST segment elevation myocardial infarction diagnosed already in the prehospital phase: results of the German Prehospital Myocardial Infarction Registry (PREMIR). Resuscitation. 2009;80(4):402-6.	No evidence of cardiac clinical network
Zeymer U, Zahn R, Gitt A, Dech M, Senges J. Aktuelle Versorgungsstruktur der Therapie des akuten Herzinfarkts in Deutschland. Der Kardiologe. 2010;4(3):231-5.	No evidence of cardiac clinical network

Table A.23: Table of studies excluded after full-text review (RQ2)

Study	Reason for exclusion
Agewall S. [New guidelines for angina pectoris]. Tidsskrift For Den Norske Laegeforening: Tidsskrift For Praktisk Medicin, Ny Raekke. 2014;134(5):510-.	Full guideline identified
Agewall S. [New guidelines for diagnosis and management of stable angina pectoris. Recommendations from the European Society of Cardiology]. Läkartidningen. 2014;111(15):680-1.	Full guideline identified
Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/acc guideline for the management of patients with Non-ST-Elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;64(24):e139-e228.	Full guideline identified
Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC guideline for the management of patients with non-st-elevation acute coronary syndromes: A report of the American college of cardiology/American heart association task force on practice guidelines. Circulation. 2014;130(25):e344-e426.	Provides no relevant outcomes
Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC guideline for the management of patients with Non-ST-Elevation acute coronary syndromes: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;64(24):2645-87.	Duplicate
Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the management of patients with non-st-elevation acute coronary syndromes: Executive summary: A report of the American college of cardiology/American heart association task force on practice guidelines. Circulation. 2014;130(25):2354-94.	Provides no relevant outcomes
Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. Journal of the American College of Cardiology. 2014;64(24):e139.	Full guideline identified
Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal Of The American College Of Cardiology. 2013;61(23):e179-e347.	Older version of guideline, standard or recommendation
Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Jr DE, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable Angina/non-ST-elevation myocardial infarction: A report of the American College of cardiology foundation/American heart association task force on practice guidelines. Circulation. 2011;123(18):e426-e579.	Older version of guideline, standard or recommendation
Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Jr DE, et al. 2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology (JACC). 2013;61(23):e179-347.	Older version of guideline, standard or recommendation
Anderson JL, Adams CD, Antman EM. Erratum: 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/Non-ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines (Journal of the American College of Cardiology (2013) 61 (e179-e347) DOI:10.1016/j.jac.2013.01.014). Journal of the American College of Cardiology. 2013;62(11):1040-1.	Older version of guideline, standard or recommendation
Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association task force on practice guidelines.	Older version of guideline, standard or recommendation

Study	Reason for exclusion
Circulation. 2008;117(2):296-329.	
Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal Of The American College Of Cardiology. 2008;51(2):210-47.	Older version of guideline, standard or recommendation
Antman. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Circulation (2008) 117, (296-329)). Circulation. 2008;117(6):e162.	Older version of guideline, standard or recommendation
Armsby L, Beekman RH, Benson L, Fagan T, Hagler DJ, Hijazi ZM, et al. SCAI expert consensus statement for advanced training programs in pediatric and congenital interventional cardiac catheterization. Catheterization and Cardiovascular Interventions. 2014;84(5):779-84.	Provides no relevant outcomes
Arntz HR, Bossaert LL, Danchin N, Nicolau N. Initial management of acute coronary syndrome: Section 5 of the european resuscitation council guidelines for resuscitation 2010. Notfall und Rettungsmedizin. 2010;13(7):621-34.	Older version of guideline, standard or recommendation
Arntz H-R, Bossaert LL, Danchin N, Nikolaou NI. European Resuscitation Council Guidelines for Resuscitation 2010 Section 5. Initial management of acute coronary syndromes. Resuscitation. 2010;81(10):1353-63.	Older version of guideline, standard or recommendation
Aroney CN, Aylward P, Chew DP, Huang N, Kelly A-M, White H, et al. 2007 addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. The Medical Journal Of Australia. 2008;188(5):302-3.	Published before 2008
Athanasiadis A, Sechtem U. Diagnostics and therapy of chronic stable coronary artery disease: New guidelines of the European Society of Cardiology. Herz. 2014;39(8):902-12.	Full guideline identified
Avezum Junior Á, Feldman A, Carvalho ACDC, Sousa ACS, Mansur ADP, Bozza AEZ, et al. V guidelines of the brazilian society of cardiology on acute myocardial infarction treatment with st segment elevation. Arquivos Brasileiros de Cardiologia. 2015;105(2):1-105.	Duplicate
Barbato E, Carrie D, Dardas P, Fajadet J, Gaul G, Haude M, et al. European expert consensus on rotational atherectomy. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2015;11(1):30-6.	No numbers provided for outcomes
Bashore TM, Balter S, Barac A, Byrne JG, Cavendish JJ, Chambers CE, et al. 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: A report of the American College of Cardiology Foundation Task Force on Expert Consensus documents developed in collaboration with the Society of Thoracic Surgeons and Society for Vascular Medicine. Journal of the American College of Cardiology. 2012;59(24):2221-305.	Duplicate
Bashore TM, Balter S, Barac A, Byrne JG, Cavendish JJ, Chambers CE, et al. 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: American College of Cardiology Foundation Task Force on expert consensus documents Society of Thoracic Surgeons Society for Vascular Medicine. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2012;80(3):E37-49.	Guideline (or other) already identified in another journal
Bassand JP, Hamm C. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology: Reply [3]. European Heart Journal. 2008;29(2):278-9.	Older version of guideline, standard or recommendation
Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). European heart journal. 2010;31(23):2915-57.	Not relevant to PCI
Becker HJ, Ollenschläger G. Interdisciplinary decision making: Expert statement on the treatment of chronic coronary artery disease. Deutsches Arzteblatt. 2009;106(15):251-2.	Not a guideline, recommendation or standard

Study	Reason for exclusion
Belgian Health Care Knowledge C. General framework for a multidisciplinary quality manual for cardiac care networks. Brussels: 2013.	Not a guideline, recommendation or standard
Blankenship JC, Gigliotti OS, Feldman DN, Mixon TA, Patel RA, Sorajja P, et al. Ad hoc percutaneous coronary intervention: a consensus statement from the Society for Cardiovascular Angiography and Interventions. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2013;81(5):748-58.	Provides no relevant outcomes
Bossaert L, O'Connor RE, Arntz HR, Brooks SC, Diercks D, Feitosa-Filho G, et al. Part 9: Acute coronary syndromes: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation. 2010;81 Suppl 1:e175-212.	Duplicate
Bossaert L, O'Connor RE, Arntz HR, Brooks SC, Diercks D, Feitosa-Filho G, et al. Part 9: Acute coronary syndromes: 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation. 2010;81(1 SUPPL.1):e175-e212.	Older version of guideline, standard or recommendation
Brieger DB, Aroney CN, Chew DP, Kelly A-M, Walters DL, Toohey CL, et al. Acute coronary syndromes: consensus recommendations for translating knowledge into action. The Medical Journal Of Australia. 2010;192(12):700-1.	Older version of guideline, standard or recommendation
Brodie BR, Sianos G, Grines CL, Antoniucci D, Mehta S, Sharma SK. Panel summary and recommendations on the role of thrombectomy with primary PCI for STEMI. Journal of Invasive Cardiology. 2010;22(SUPPL. B):34B-5B.	Provides no relevant outcomes
Burt DR, Ghaemmaghami C, Rosen R, Gimple L, O'Connor R. Standardized stemi alert protocols and interfacility transfer guidelines optimize stemi reperfusion times. Circulation. 2011;124(21).	Not a guideline, recommendation or standard
Burzotta F, Lassen JF, Banning AP, Lefèvre T, Hildick-Smith D, Chieffo A, et al. Percutaneous coronary intervention in left main coronary artery disease: The 13th consensus document from the European Bifurcation Club. EuroIntervention. 2018;14(1):112-20.	No numbers provided for outcomes
Canadian Institute for Health I. Cardiac Care Quality Indicators Report. 2017.	Not a guideline, recommendation or standard
Cannon CP, Brindis RG, Chaitman BR, Cohen DJ, Cross Jr JT, Drozda Jr JP, et al. 2013 ACCF/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (writing committee to develop acute coronary syndromes and coronary artery disease clinical data standards). Critical Pathways in Cardiology. 2013;12(2):65-105.	Guideline (or other) already identified in another journal
Cannon CP, Brindis RG, Chaitman BR, Cohen DJ, Cross JT, Drozda JP, et al. 2013 ACCF/AHA Key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: A report of the American college of cardiology foundation/American Heart Association Task force on Clinical Data Standards (Writing committee to develop acute coronary syndromes and coronary artery disease clinical data standards). Circulation. 2013;127(9):1052-89.	Provides no relevant outcomes
Cantero JCT, Aroca JMB. The European Association for Cardio-Thoracic Surgery Guidelines onmyocardial revascularization. Second part. Cirugia Cardiovascular. 2015;22(1):39-43.	Older version of guideline, standard or recommendation
Carville S, Harker M, Henderson R, Gray H. Acute management of myocardial infarction with ST-segment elevation: summary of NICE guidance. BMJ: British Medical Journal. 2013;347(7916):34-5.	Full guideline identified
Carville SF, Henderson R, Gray H. The acute management of ST-segment-elevation myocardial infarction. Clinical Medicine. 2015;15(4):362-7.	Full guideline identified
Cesar LA, Ferreira JF, Armaganijan D, Gowdak LH, Mansur AP, Bodanese LC, et al. Guideline for stable coronary artery disease. Arquivos brasileiros de cardiologia. 2014;103(2 Suppl 2):1-56.	No numbers provided for outcomes
Chambers CE, Dehmer GJ, Cox DA, Harrington RA, Babb JD, Popma JJ, et al. Defining the length of stay following percutaneous coronary intervention: an expert	Provides no relevant outcomes

Study	Reason for exclusion
consensus document from the Society for Cardiovascular Angiography and Interventions. Endorsed by the American College of Cardiology Foundation. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2009;73(7):847-58.	
Charpentier S, Savary D, Lapostolle F, Chouihed T, Bonnefoy E, Manzo-Silberman S, et al. Guidelines of the European Society of Cardiology for the management of non-ST elevation acute coronary syndrome. Annales Francaises de Medecine d'Urgence. 2014;4(1):56-64.	Older version of guideline, standard or recommendation
Chew D, Aroney C, Aylward P, White H, Tideman P, Kelly A, et al. 2011 addendum to the guidelines for the management of acute coronary syndromes 2006. Heart Lung and Circulation. 2011;20:S111-S2.	Guideline (or other) already identified in another journal
Chew DP, Aroney CN, Aylward PE, Kelly A-M, White HD, Tideman PA, et al. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. Heart, Lung & Circulation. 2011;20(8):487-502.	Duplicate
Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, et al. Corrigendum to 'National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016' (Heart Lung and Circulation (2016) 25(9) (895–951) (S1443950616310617) (10.1016/j.hlc.2016.06.789)). Heart Lung and Circulation. 2017;26(10):1117.	Not a guideline, recommendation or standard
Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, et al. Corrigendum to 'National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016' Heart Lung and Circulation volume 25, (2016) 898 - 952. Heart, Lung & Circulation. 2017;26(10):1117-.	Older version of guideline, standard or recommendation
Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. The Medical journal of Australia. 2016;205(3):128-33.	Full guideline identified
China Society of Cardiology of Chinese Medical A, Editorial Board of Chinese Journal of C. [Guideline for diagnosis and treatment of patients with ST-elevation myocardial infarction]. Zhonghua xin xue guan bing za zhi [Chinese journal of cardiovascular diseases]. 2010;38(8):675-90.	Older version of guideline, standard or recommendation
Claeys MJ, Gevaert S, De Meester A, Evrard P, Legrand V, Vrints C, et al. Implementation of reperfusion therapy in ST-segment elevation myocardial infarction a policy statement from the Belgian Society of Cardiology (BSC), the Belgian Interdisciplinary Working Group on Acute Cardiology (BIWAC) and the Belgian Working Group on Interventional Cardiology (BWGIC). Acta Cardiologica. 2009;64(4):541-5.	Older version of guideline, standard or recommendation
Claeys MJ. Guidelines on the management of stable coronary artery disease. Acta Cardiologica. 2014;69(1):51-2.	Full guideline identified
Clinical Practice Guidelines S. Clinical practice guidelines - Management of unstable angine/non-ST segment elevation myocardial infarction (UA/NSTEMI). Putrajaya: Ministry of Health Malaysia, 2011.	Provides no relevant outcomes
Cortese B, Berti S, Biondi-Zoccai G, Colombo A, Limbruno U, Bedogni F, et al. Drug-coated balloon treatment of coronary artery disease: a position paper of the Italian Society of Interventional Cardiology. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2014;83(3):427-35.	Provides no relevant outcomes
Davis J. The Society of Invasive Cardiovascular Professionals New 2015 Educational Guidelines for Invasive Cardiovascular Technology Personnel in the Cardiovascular Catheterization Laboratory. EP Lab Digest. 2015;15(6):24-9.	Provides no relevant outcomes
de Oliveira MT, de Paula LJC, Marcolino MS, Canesin MF. Executive summary – Guideline on telecardiology in the care of patients with acute coronary syndrome and other cardiac diseases. Arquivos Brasileiros de Cardiologia. 2015;105(2):105-11.	Full guideline identified
Dehmer GJ, Blankenship JC, Cilingiroglu M, Dwyer JG, Feldman DN, Gardner TJ, et al. SCAI/ACC/AHA Expert consensus document: 2014 Update on Percutaneous Coronary Intervention Without On-Site Surgical Backup. Catheterization and	Guideline (or other) already identified in another journal

Study	Reason for exclusion
Cardiovascular Interventions. 2014;84(2):169-87.	
Einecke D. New guideline for heart infarction: What is new and where the biggest deficits exist. MMW-Fortschritte der Medizin. 2012;154(SUPPL.3):24-5.	Full guideline identified
El-Deeb MH, Al Riyami AM, Al Riyami AA, Sulaiman KJ, Shahrabani R, Al Mukhaini M, et al. 2012 Oman heart association simplified guidelines for the management of patients with unstable angina/Non-ST-elevation myocardial infarction. Critical Pathways in Cardiology. 2012;11(3):139-46.	Provides no relevant outcomes
Everaert B, Wykrzykowska JJ, Koolen J, van der Harst P, den Heijer P, Henriques JP, et al. Recommendations for the use of bioresorbable vascular scaffolds in percutaneous coronary interventions. Netherlands Heart Journal. 2017;25(7-8):419-28.	Provides no relevant outcomes
Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Canadian Journal of Cardiology. 2017;33(11):1342-433.	Provides no relevant outcomes
Feitosa-Filho GS, Baracioli LM, Barbosa CJ, Franci A, Timerman A, Soares Piegas L, et al. SBC guidelines on unstable angina and non-ST-elevation myocardial infarction: executive summary. Arquivos brasileiros de cardiologia. 2015;105(3):214-27.	Provides no relevant outcomes
Feres F, Costa RA, Siqueira D, Costa JR, Jr., Chamie D, Staico R, et al. Arquivos brasileiros de cardiologia. 2017;109(1 Suppl 1):1-81.	Full guideline identified
Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2014;130(19):1749-67.	Guideline (or other) already identified in another journal
Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2014;64(18):1929-49.	Provides no relevant outcomes
Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. Journal of the American College of Cardiology. 2012;60(24):e44-e164.	Older version of guideline, standard or recommendation
Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart diseass. Circulation. 2012;126(25):e354-e471.	Older version of guideline, standard or recommendation
Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American college of cardiology/American heart association task force on practice guidelines. Journal of the American College of Cardiology. 2014;64(22):e77-e137.	Guideline (or other) already identified in another journal
Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: Executive summary a report of the american college of cardiology/american heart association task force on practice guidelines. Circulation. 2014;130(24):2215-45.	Not relevant to PCI
Foedisch MJ, Viehoefer A. Standard operating procedures: Therapeutic hypothermia in CPR and post-resuscitation care. Critical Care. 2012;16.	Not a guideline, recommendation or standard
Forge BH, Brieger DB, Chew D, Aroney C, Aylward P, Walters D, et al. Acute coronary syndromes: Consensus recommendations for translating knowledge into	Not a guideline, recommendation or

Study	Reason for exclusion
action. Medical Journal of Australia. 2010;193(9):550-3.	standard
Forge BH. Acute coronary syndromes: consensus recommendations for translating knowledge into action. The Medical Journal Of Australia. 2010;193(9):550-1.	Older version of guideline, standard or recommendation
Forge BH. The 'acute coronary syndromes: Consensus recommendations for translating knowledge into action' position statement is based on a false premise. Medical Journal of Australia. 2010;192(12):696-9.	Older version of guideline, standard or recommendation
Fukuhara R, Fujiwara H. Japanese guidelines for elective percutaneous coronary intervention in patients with stable coronary disease. Nihon rinsho Japanese journal of clinical medicine. 2016;74 Pt 1:347-52.	Could not obtain full-text
Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Journal of the American College of Cardiology. 2013;61(4):e78.	Older version of guideline, standard or recommendation
German Medical Association Kassenärztliche Confederation working group of the scientific Medical S. Disease Management Guideline Chronic CHD - Kurzfas- sung.	Provides no relevant outcomes
Ghimire G, Gupta A, Hage FG. Guidelines in review: 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Journal of Nuclear Cardiology. 2014;21(1):190-1.	Older version of guideline, standard or recommendation
Gonçalvesová E. The 'Recommendations for revascularization'. Cardiology Letters. 2011;20(5):431-2.	Could not obtain full-text
Goodman SG, Menon V, Cannon CP, Steg G, Ohman EM, Harrington RA. Acute ST-segment elevation myocardial infarction: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008;133(6 SUPPL. 6):708S-75S.	Provides no relevant outcomes
Goodman. Acute ST-segment elevation myocardial infarction: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition) (Chest (2008) 133, SUPPL, (708S-775S)). Chest. 2008;134(4):892.	Duplicate
Goto Y. [Guidelines for the management of patients with acute myocardial infarction (ST-elevation type)]. Nihon rinsho Japanese journal of clinical medicine. 2011;69 Suppl 9:573-82.	Could not obtain full-text
Gürmen T, Arat-Özkan A. 2010 Guidelines on myocardial revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. Turk Kardiyoloji Dernegi Arsivi. 2011;39(1):5-8.	Older version of guideline, standard or recommendation
Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2011;32(23):2999-3054.	Older version of guideline, standard or recommendation
Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Revista Espanola de Cardiologia. 2012;65(2):173.e1-.e55.	Older version of guideline, standard or recommendation
Harold JG, Bass TA, Bashore TM, Brindis RG, Brush JE, Burke JA, et al. ACCF/AHA/SCAI 2013 update of the clinical competence statement on coronary artery interventional procedures: A report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training (Writing Committee to Revise the 2007 Clinical Competence Statement on Cardiac Interventional Procedures). Circulation. 2013;128(4):436-72.	Guideline (or other) already identified in another journal
Hauk L. Management of Non-ST Elevation Acute Coronary Syndrome: A Guideline from the AHA and ACC. American Family Physician. 2015;92(2):151-3.	Full guideline identified
Hazinski MF, Nolan JP, Aickin R, Bhanji F, Billi JE, Callaway CW, et al. Part 1: Executive summary: 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation. 2015;132:S2-S39.	Full guideline identified
Hazinski MF, Nolan JP, Billi JE, Bottiger BW, Bossaert L, de Caen AR, et al. Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2010;122(16 Suppl 2):S250-75.	Older version of guideline, standard or recommendation
Hildick-Smith D, Lassen JF, Albiero R, Lefevre T, Darremont O, Pan M, et al. Consensus from the 5th European Bifurcation Club meeting. EuroIntervention :	Provides no relevant outcomes

Study	Reason for exclusion
journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2010;6(1):34-8.	
Hoekstra J, Cohen M, Giugliano R, Granger CB, Gurbel PA, Hollander JE, et al. Expert consensus on treatment strategies in non- ST-segment elevation acute coronary syndromes in patients undergoing percutaneous coronary intervention--an evidence-based review of clinical trial results and treatment guidelines from an emergency medicine perspective: report on a roundtable discussion. The American Journal Of Emergency Medicine. 2009;27(6):720-8.	Provides no relevant outcomes
Hori S. [New evidences in the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care with Treatment Recommendations]. Nippon rinsho Japanese journal of clinical medicine. 2011;69(4):605-11.	Older version of guideline, standard or recommendation
Hricák V. Correct direction and significant drift in management of acute myocardial infarction (STEMI) in Slovakia: Slovaks-2 and first collective guidelines of the Slovak society of cardiology and the society of emergency and catastrophe medicine. Cardiology Letters. 2013;22(2):101-3.	Could not obtain full-text
Huber K, Gaul G, Kaff A, Laggner AN, Mlczoch J, Weber H, et al. Treatment of acute heart infarction 2008: International guidelines and the Vienna model. Journal fur Kardiologie. 2008;15(5-6):109-12.	Not a guideline, recommendation or standard
Hunyadi-Antičević S, Protić A, Patrk J, Filipović-Grčić B, Puljević D, Majhen-Ujević R, et al. EUROPEAN RESUSCITATION COUNCIL GUIDELINES FOR RESUSCITATION 2015. Lijecnicki vjesnik. 2016;138(11-12):305-21.	Guideline (or other) already identified in another journal
Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Kardiologia polska. 2018;76(2):229-313.	Duplicate
Ibánez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Revista Espanola De Cardiologia (English Ed). 2017;70(12):1082-.	Guideline (or other) already identified in another journal
Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-77.	Guideline (or other) already identified in another journal
Ibáñez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. ESC 2017 guidelines on the treatment of acute myocardial infarction in patients with ST segment elevation. Revista Espanola de Cardiologia. 2017;70(12):1082.e1-.e61.	Guideline (or other) already identified in another journal
Ijsselmuiden AJJ, Zwaan EM, Oemrawsingh RM, Bom MJ, Dankers FJWM, de Boer MJ, et al. Appropriate use criteria for optical coherence tomography guidance in percutaneous coronary interventions : Recommendations of the working group of interventional cardiology of the Netherlands Society of Cardiology. Netherlands Heart Journal: Monthly Journal Of The Netherlands Society Of Cardiology And The Netherlands Heart Foundation. 2018;26(10):473-83.	Not a guideline, recommendation or standard
Ince H, Zeus T. Heart Valve Disease - Update ESC guideline 2017. Deutsche Medizinische Wochenschrift. 2018;143(24):1765-9.	Not relevant to PCI
Indolfi C. The ESC/EACTS guidelines on myocardial revascularization: The interventional cardiologist's view. Giornale Italiano di Cardiologia. 2011;12(4):245-50.	Full guideline identified
Jacques H. Setting minimum standards for interventional cardiology in France. European Heart Journal. 2012;33(19):2375-6.	Not a guideline, recommendation or standard
Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2012;126(7):875-910.	Older version of guideline, standard or recommendation
Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey Jr DE, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007	Older version of guideline, standard or recommendation

Study	Reason for exclusion
guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2012;60(7):645-81.	
Jobe RL, Mann T. Transradial consensus statement: appropriateness ratings for patient selection and physicians' performing procedures. Journal of the Indian Medical Association. 2009;107(9):587-8.	Could not obtain full-text
Kakou-Guikahue M, N'Guetta R, Anzouan-Kacou JB, Kramoh E, N'Dori R, Ba SA, et al. Optimizing the management of acute coronary syndromes in sub-Saharan Africa: A statement from the AFRICARDIO 2015 Consensus Team. Archives of cardiovascular diseases. 2016;109(6-7):376-83.	Provides no relevant outcomes
Kastrati A, Caforio ALP, Bucciarelli-Ducci C, Varenhorst C, Prescott E, Crea F, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2017;39(2):119-77.	Older version of guideline, standard or recommendation
Klein LW, Blankenship JC, Kolansky DM, Dean LS, Naidu SS, Chambers CE, et al. SCAI position statement concerning coverage policies for percutaneous coronary interventions based on the appropriate use criteria. Catheterization and Cardiovascular Interventions. 2016;87(6):1127-9.	Provides no relevant outcomes
Klein LW, Ho KKL, Singh M, Anderson HV, Hillegass WB, Uretsky BF, et al. Quality assessment and improvement in interventional cardiology: A position statement of the society of cardiovascular angiography and interventions, Part II: Public reporting and risk adjustment. Catheterization and Cardiovascular Interventions. 2011;78(4):493-502.	Older version of guideline, standard or recommendation
Klein LW, Uretsky BF, Chambers C, Anderson HV, Hillegass WB, Singh M, et al. Quality assessment and improvement in interventional cardiology: a position statement of the Society of Cardiovascular Angiography and Interventions, part 1: standards for quality assessment and improvement in interventional cardiology. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2011;77(7):927-35.	Older version of guideline, standard or recommendation
Kolh P, Wijns W, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization. European Journal of Cardio-thoracic Surgery. 2010;38(SUPPL. 1):S1-S52.	Older version of guideline, standard or recommendation
Kolh P, Wijns W. Joint ESC/EACTS guidelines on myocardial revascularization. Heart Surgery Forum. 2011;14:S3.	Older version of guideline, standard or recommendation
Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. European Journal of Cardio-thoracic Surgery. 2014;46(4):517-92.	Older version of guideline, standard or recommendation
Kolh P, Windecker S. ESC/EACTS myocardial revascularization guidelines 2014. European heart journal. 2014;35(46):3235-6.	Older version of guideline, standard or recommendation
Koskinas KC, Windecker S. 2014 ESC/EACTS guidelines on myocardial revascularisation. Kardiovaskulare Medizin. 2016;19(6):170-5.	Older version of guideline, standard or recommendation
Krumholz HM, Anderson JL, Bachelder BL, Fesmire FM, Fihn SD, Foody JM, et al. ACC/AHA 2008 performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to develop performance measures for ST-elevation and non-ST-elevation myocardial infarction): developed in collaboration with the American Academy of Family Physicians and the American College of Emergency Physicians: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Society for Cardiovascular Angiography and Interventions, and Society of Hospital Medicine. Circulation. 2008;118(24):2596-648.	Older version of guideline, standard or recommendation
Kushner FG, Hand M, Smith Jr SC, King ISB, Anderson JL, Antman EM, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update). Journal of the American	Older version of guideline, standard or recommendation

Study	Reason for exclusion
College of Cardiology. 2009;54(23):2205-41.	
Kushner FG, Hand M, Smith SC, Jr., King SB, 3rd, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Catheterization And Cardiovascular Interventions: Official Journal Of The Society For Cardiac Angiography & Interventions. 2009;74(7):E25-E68.	Older version of guideline, standard or recommendation
Kushner FG, Hand M, Smith SC, King SB, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with st-elevation myocardial infarction (Updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (Updating the 2005 Guideline and 2007 Focused Update). Circulation. 2009;120(22):2271-306.	Older version of guideline, standard or recommendation
Kushner. Erratum: 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update). Circulation. 2010;121(12):e257.	Older version of guideline, standard or recommendation
Lempereur M, Moonen M, Gach O, Lancellotti P. 2011 ESC guidelines for the management of acute coronary syndromes without ST segment elevation. Revue Medicale de Liege. 2012;67(1):8-10.	Older version of guideline, standard or recommendation
Levine GM, Bates ER, Blankenship JC. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions (Journal of the American College of Cardiology (2011) 58 (e44-122) DOI:10.1016/j.jacc.2011.08.007). Journal of the American College of Cardiology. 2012;59(11):1042.	Older version of guideline, standard or recommendation
Levine GM, Bates ER, Blankenship JC. Erratum: 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions (Journal of the American College of Cardiology (2011) 58 (2550-2583) DOI:10.1016/j.jacc.2011.08. 008). Journal of the American College of Cardiology. 2012;59(11):1042.	Older version of guideline, standard or recommendation
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):e574-e651.	Older version of guideline, standard or recommendation
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Journal Of The American College Of Cardiology. 2011;58(24):e44-e122.	Older version of guideline, standard or recommendation
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheterization And Cardiovascular Interventions: Official Journal Of The Society For Cardiac Angiography & Interventions. 2013;82(4):E266-E355.	Older version of guideline, standard or recommendation
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheterization and Cardiovascular Interventions. 2011;45(4).	Older version of guideline, standard or recommendation
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011	Older version of

Study	Reason for exclusion
ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Journal of the American College of Cardiology. 2011;58(24):2550-83.	guideline, standard or recommendation
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheterization and Cardiovascular Interventions. 2012;79(3):453-95.	Older version of guideline, standard or recommendation
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: Executive summary: A report of the American College of Cardiology Foundation/American HeartA sociation Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):2574-609.	Older version of guideline, standard or recommendation
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients with ST-Elevation Myocardial Infarction An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Journal of the American College of Cardiology. 2016;67(10):1235-50.	Provides no relevant outcomes
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction. An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. 2016;67(10):1235-50.	Duplicate
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Circulation. 2016;133(11):1135-47.	Guideline (or other) already identified in another journal
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial Infarction: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheterization and Cardiovascular Interventions. 2016;87(6):1001-19.	Guideline (or other) already identified in another journal
Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarctionAn update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction a report of the American college of cardiology/American Heart Association task force on clinical practice guidelines and the society for cardiovascular angiography and interventions. Circulation. 2016;133(11):1135-47.	Guideline (or other) already identified in another journal
Levine GN, O'Gara PT. Correction: 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients with ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction (J Am Coll Cardiol (2016) 67 (1235-50)). Journal of the American College of Cardiology. 2016;67(12):1506.	Not a guideline, recommendation or standard
Levine. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention (Circulation (2011) 124, (e574-e651)). Circulation. 2012;125(8):e412.	Older version of guideline, standard or

Study	Reason for exclusion
	recommendation
Levine. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: Executive summary (Circulation (2011) 124, (2574-2609)). Circulation. 2012;125(8):e411.	Older version of guideline, standard or recommendation
Levisman J, Price MJ. Update on the guidelines for the management of ST-elevation myocardial infarction. American Journal of Cardiology. 2015;115(5):3A-9A.	Full guideline identified
Li YH, Wang YC, Liu JC, Lee CH, Chen CC, Hsieh IC, et al. 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the management of non ST-segment elevation acute coronary syndrome. Journal of the Formosan Medical Association. 2018;117(9):766-90.	No numbers provided for outcomes
Linden B. A quality standard for adults who have stable angina. British Journal of Cardiac Nursing. 2013;8(5):216-7.	Full guideline identified
Linden B. ESC guidelines for acute coronary syndromes without ST elevation. British Journal of Cardiac Nursing. 2011;6(11):547-8.	Not a guideline, recommendation or standard
Linden B. European societies' guideline on myocardial revascularization. British Journal of Cardiac Nursing. 2011;6(8):400-1.	Not a guideline, recommendation or standard
Linden B. NICE guidance on ST-segment elevation myocardial infarction. British Journal of Cardiac Nursing. 2013;8(9):417-8.	Full guideline identified
Linden B. NICE guidance on unstable angina and NSTEMI. British Journal of Cardiac Nursing. 2010;5(6):302-3.	Full guideline identified
Linden B. NICE guideline on management of stable angina. British Journal of Cardiac Nursing. 2011;6(10):478-9.	Not a guideline, recommendation or standard
Linden B. Recommendations for care of patients with acute coronary syndromes. British Journal of Cardiac Nursing. 2015;10(1):8-9.	Full guideline identified
Linden B. Recommendations for myocardial revascularisation for patients with coronary artery disease. British Journal of Cardiac Nursing. 2015;10(2):62-3.	Older version of guideline, standard or recommendation
Luckraz H, Norell M, Buch M, James R, Cooper G. Structure and functioning of a multidisciplinary 'Heart Team' for patients with coronary artery disease: Rationale and recommendations from a joint BCS/BCIS/SCTS working group. European Journal of Cardio-thoracic Surgery. 2015;48(4):524-9.	No numbers provided for outcomes
Lüscher TF. Optimizing percutaneous coronary interventions: Heart Team, SYNTAX II Score, physiology and imaging guidance, modern stents, and guideline-based medication. European Heart Journal. 2017;38(42):3109-13.	Not a guideline, recommendation or standard
Lüscher TF. ST-segment elevation myocardial infarction: The new ESC Guidelines. European Heart Journal. 2018;39(2):75-8.	Full guideline identified
Maier SKG, Thiele H, Zahn R, Sefrin P, Naber CK, Scholz KH, et al. Recommendations for the organization of acute myocardial infarction networks. Kardiologe. 2014;8(1):36-44.	Not a guideline, recommendation or standard
Mancini GBJ, Gosselin G, Chow B, Kostuk W, Stone J, Yvorchuk KJ, et al. Canadian Cardiovascular Society guidelines for the diagnosis and management of stable ischemic heart disease. The Canadian Journal Of Cardiology. 2014;30(8):837-49.	Provides no relevant outcomes
Masoudi FA, Bonow RO, Brindis RG, Cannon CP, DeBuhr J, Fitzgerald S, et al. ACC/AHA 2008 Statement on Performance Measurement and Reperfusion Therapy. Journal of the American College of Cardiology. 2008;52(24):2100-12.	Not a guideline, recommendation or standard
Masoudi FA, Bonow RO, Brindis RG, Cannon CP, Debuhr J, Fitzgerald S, et al. ACC/AHA 2008 statement on performance measurement and reperfusion therapy: a report of the ACC/AHA Task Force on Performance Measures (Work Group to address the challenges of performance measurement and reperfusion therapy). Circulation. 2008;118(24):2649-61.	Guideline (or other) already identified in another journal
Mathias JM. New consensus statement for cardiac cath labs. OR manager. 2012;28(7):24, 6.	Could not obtain full-text
Mattos LA, Lemos Neto PA, Rassi Jr A, Marin-Neto JA, Sousa AGDMR, Devito FS, et al. Guidelines of the Brazilian Society of Cardiology - Percutaneous coronary intervention and joint diagnostic methods in interventional cardiology (II Edition -	Could not be accurately translated to English

Study	Reason for exclusion
2008). Arquivos Brasileiros de Cardiologia. 2008;91(6 SUPPLEMENT):1-58.	
McGillion M, Arthur HM, Cook A, Carroll SL, Victor JC, L'Allier PL, et al. Management of Patients With Refractory Angina: Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines. Canadian Journal of Cardiology. 2012;28(2 SUPPL.):S20-S41.	Not relevant to PCI
McGillion M, L'Allier PL, Arthur H, Watt-Watson J, Svorkdal N, Cosman T, et al. Recommendations for advancing the care of Canadians living with refractory angina pectoris: a Canadian Cardiovascular Society position statement. The Canadian Journal Of Cardiology. 2009;25(7):399-401.	Older version of guideline, standard or recommendation
Mechem CC, Goodloe JM, Richmond NJ, Kaufman BJ, Pepe PE. Resuscitation center designation: Recommendations for emergency medical services practices. Prehospital Emergency Care. 2010;14(1):51-61.	No numbers provided for outcomes
Mishra S, Ray S, Dalal JJ, Sawhney JPS, Ramakrishnan S, Nair T, et al. Management standards for stable coronary artery disease in India. Indian Heart Journal. 2016;68:S31-S49.	Provides no relevant outcomes
Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease. European Heart Journal. 2013;34(38):2949-3003.	Provides no relevant outcomes
Morrison LJ, Deakin CD, Morley PT, Callaway CW, Kerber RE, Kronick SL, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Circulation. 2010;122(16 SUPPL. 2):S345-S421.	Older version of guideline, standard or recommendation
Naidu SS, Rao SV, Blankenship J, Cavendish JJ, Farah T, Moussa I, et al. Clinical expert consensus statement on best practices in the cardiac catheterization laboratory: Society for cardiovascular angiography and interventions. Catheterization and Cardiovascular Interventions. 2012;80(3):456-64.	Provides no relevant outcomes
Nef H, Renker M, Hamm CW. ESC/EACTS guidelines on myocardial revascularization: Amendments 2014. Herz. 2014;39(8):913-8.	Older version of guideline, standard or recommendation
Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Kardiologia polska. 2018;76(12):1585-664.	Guideline (or other) already identified in another journal
Neumar RW, Shuster M, Callaway CW, Gent LM, Atkins DL, Bhanji F, et al. Part 1: Executive summary: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132(18):S315-S67.	Full guideline identified
Nichol G, Aufderheide TP, Eigel B, Neumar RW, Lurie KG, Bufalino VJ, et al. Regional systems of care for out-of-hospital cardiac arrest: A policy statement from the american heart association. Circulation. 2010;121(5):709-29.	Not a guideline, recommendation or standard
Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJ, Franci A, et al. [Guidelines of Sociedade Brasileira de Cardiologia for Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction (II Edition, 2007) 2013-2014 Update]. Arquivos brasileiros de cardiologia. 2014;102(3):1-61.	Duplicate
Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJDG, Franci A, et al. Guidelines of the Brazilian Society of Cardiology on unstable angina and acute myocardial infarction without ST segment elevation (II Edition, 2007) - Update 2013/2014. Arquivos Brasileiros de Cardiologia. 2014;102(3 SUPPL. 1):1-61.	Could not be accurately translated to English
Nikolaou NI, Arntz HR, Bellou A, Beygui F, Bossaert LL, Cariou A. Initial management of acute coronary syndromes: Section 8 of the European Resuscitation Council Guidelines for Resuscitation 2015. Notfall und Rettungsmedizin. 2015;18(8):984-1002.	Guideline (or other) already identified in another journal
Noc M, Fajadet J, Lassen JF, Kala P, Maccarthy P, Olivecrona GK, et al. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: A consensus statement from the european association for percutaneous cardiovascular interventions (eapci)/stent for life (sfl) groups. EuroIntervention. 2014;10(1):31-7.	Provides no relevant outcomes
Nolan JP, Hazinski MF, Billi JE, Boettiger BW, Bossaert L, de Caen AR, et al. Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Resuscitation. 2010;81 Suppl 1:e1-25.	Older version of guideline, standard or recommendation
Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VRM, Deakin CD, et al. European	Guideline (or other)

Study	Reason for exclusion
Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Medicine. 2015;41(12):2039-56.	already identified in another journal
Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VRM, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015. Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015;95:202-22.	Provides no relevant outcomes
Ochi M. Overview: Japanese guidelines for myocardial revascularization to treat stable ischemic heart disease 2012. General Thoracic and Cardiovascular Surgery. 2013;61(5):246-53.	Full guideline identified
O'Connor RE, Bossaert L, Arntz HR, Brooks SC, Diercks D, Feitosa-Filho G, et al. Part 9: Acute coronary syndromes: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Circulation. 2010;122(16 SUPPL. 2):S422-S65.	Older version of guideline, standard or recommendation
O'Connor RE, Brady W, Brooks SC, Diercks D, Egan J, Ghaemmaghami C, et al. Part 10: Acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(SUPPL. 3):S787-S817.	Older version of guideline, standard or recommendation
O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology (JACC). 2013;61(4):e78-e140.	Older version of guideline, standard or recommendation
O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362-e425.	Older version of guideline, standard or recommendation
O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):529-55.	Older version of guideline, standard or recommendation
O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheterization And Cardiovascular Interventions: Official Journal Of The Society For Cardiac Angiography & Interventions. 2013;82(1):E1-E27.	Older version of guideline, standard or recommendation
O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, De Lemos JA, et al. 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction: Executive summary: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. Journal of the American College of Cardiology. 2013;61(4):485-510.	Older version of guideline, standard or recommendation
O'Gara PT, Kushner FG, Ascheim DD. Erratum: 2010 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines (Journal of the American College of Cardiology (2013) 61 (485-510) DOI:10.1016/j.jacc.2012.11.018). Journal of the American College of Cardiology. 2013;62(11):1039.	Older version of guideline, standard or recommendation
Ošťádal P, Rokyta R, Balík M, Bělohlávek J, Cvachovec K, Černý V, et al. Cardiac Arrest Centers: Joint statement of Czech Professional Societies: Czech Acute Cardiac Care Association of the Czech Society of Cardiology, Czech Resuscitation Council, Czech Society of Intensive Care Medicine ČLS JEP, Czech Society of Anesthesiology, Resuscitation and Intensive Care Medicine ČLS JEP, and Society for Emergency and Disaster Medicine ČLS JEP. Cor et Vasa. 2017;59(2):e196-e9.	Provides no relevant outcomes
Ozaki Y, Katagiri Y, Onuma Y, Amano T, Muramatsu T, Kozuma K, et al. CVIT expert consensus document on primary percutaneous coronary intervention (PCI)	No numbers provided for outcomes

Study	Reason for exclusion
for acute myocardial infarction (AMI) in 2018. Cardiovascular intervention and therapeutics. 2018;33(2):178-203.	
Palisaitis D, Love M, Zimmerman R, Radhakrishnan S, Welsh R, Saw J, et al. 2010 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiologists Guidelines for Training and Maintenance of Competency in Adult Interventional Cardiology. Canadian Journal of Cardiology. 2011;27(6):865-7.	Provides no relevant outcomes
Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS, Dehmer GJ, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: American College of Cardiology Foundation Appropriate Use Criteria Task Force Society for Cardiovascular Angiography and Interventions American Association for Thoracic Surgery American Heart Association. Catheterization and Cardiovascular Interventions. 2012;80(3):E50-E81.	Provides no relevant outcomes
Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes : A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2017;24(2):439-63.	No numbers provided for outcomes
Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease : A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2017;24(5):1759-92.	No numbers provided for outcomes
Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. Correction to: ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2018;25(6):2191-2.	Not a guideline, recommendation or standard
Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA, Masoudi FA, et al. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association Tomography. Journal of the American College of Cardiology. 2012;59(9):857-81.	Older version of guideline, standard or recommendation
Patrick TOG, Frederick GK, Deborah DA, Donald EC, Mina KC, James AdL, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Circulation. 2013;127(4):e362-e425.	Older version of guideline, standard or recommendation
Peberdy MA, Donnino MW, Callaway CW, DiMaio JM, Geocadin RG, Ghaemmaghami CA, et al. Impact of percutaneous coronary intervention performance reporting on cardiac resuscitation centers a scientific statement from the american heart association. Circulation. 2013;128(7):762-73.	Provides no relevant outcomes
Pedrazzini GB, Ferrari E, Zellweger M, Genoni M. Heart Team: Joint Position of the Swiss Society of Cardiology and the Swiss Society of Cardiac Surgery. The Thoracic and cardiovascular surgeon. 2017;65(7):519-23.	No numbers provided for outcomes
Perings SM, Bosch R, Eggeling T, Hennersdorf M, Graf La Rosee K, Korte T, et al. [European guidelines on myocardial revascularization]. Herz. 2011;36(3):265-6.	Older version of guideline, standard or recommendation
Polášek R, Nedbal P, Jaworski L, Kučera P, Skoupá K, Hanuliaková J, et al. Indications for ICD implantation in the primary prevention of sudden cardiac death	Not relevant to PCI

Study	Reason for exclusion
after a STEMI. The impact of a change in the Czech Society of Cardiology guidelines on the number of patients scheduled for the procedure. Cor et Vasa. 2010;52(1-2):36-8.	
Porela P, Mantyla P, Blek-Vehkaluoto M, Ilveskoski E, Juvonen T, Kujanpaa T, et al. [Update on Current Care Guidelines. Current Care Guideline: Stable Coronary Artery Disease]. Duodecim; laaketieteellinen aikakauskirja. 2015;131(10):967-8.	Provides no relevant outcomes
Qaseem A, Fihn SD, Williams S, Dallas P, Owens DK, Shekelle P. Management of stable ischemic heart disease: Summary of a clinical practice guideline from the American College of Physicians/American College of Cardiology Foundation/ American Heart Association/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons. Annals of Internal Medicine. 2012;157(10):735-43.	Full guideline identified
Quaile A. SIGN guidelines: current management of stable angina. British Journal of Cardiac Nursing. 2018;13(7):322-3.	Full guideline identified
Quaile A. SIGN: initial management of acute coronary syndrome. British Journal of Cardiac Nursing. 2018;13(4):166-7.	Not a guideline, recommendation or standard
Quaile A. Updated recommendations for managing patients with STEMI. British Journal of Cardiac Nursing. 2018;13(2):62-3.	Not a guideline, recommendation or standard
Quraishi AuR, Lambert LJ, Madan M, Gong Y, Forsey A, Galbraith D, et al. Quality of Care for Percutaneous Coronary Intervention: Development of Canadian Cardiovascular Society Quality Indicators. Canadian Journal of Cardiology. 2016;32(12):1570-3.	Full guideline identified
Reifart N. European guidelines for myocardial revascularization: Summary and interpretation. Herz. 2011;36(3):265-6.	Full guideline identified
Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Kardiologia polska. 2015;73(12):1207-94.	Guideline (or other) already identified in another journal
Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-segment Elevation. Revista Espanola De Cardiologia (English Ed). 2015;68(12):1125-.	Guideline (or other) already identified in another journal
Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Russian Journal of Cardiology. 2016;131(3):9-63.	Provides no relevant outcomes
Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Giornale Italiano di Cardiologia. 2016;17(10):831-72.	Guideline (or other) already identified in another journal
Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the european society of cardiology (ESC). European Heart Journal. 2016;37(3):267-315.	Guideline (or other) already identified in another journal
Rolley JX, Salamonson Y, Dennison CR, Davidson PM. Development of clinical practice guidelines for the nursing care of people undergoing percutaneous coronary interventions: An Australian & New Zealand collaboration. Australian Critical Care. 2010;23(4):177-87.	Not a guideline, recommendation or standard
Rolley JX, Salamonson Y, Wensley C, Dennison CR, Davidson PM. Nursing clinical practice guidelines to improve care for people undergoing percutaneous coronary interventions. Australian Critical Care. 2011;24(1):18-38.	Provides no relevant outcomes
Salvi A, Bolognese L, Cavallini C, De Servi S, Giordano A, Marzocchi A, et al. Italian Society of Interventional Cardiology standards and guidelines for the cardiac catheterization laboratory. Giornale Italiano di Cardiologia. 2008;9(9):643-51.	Could not obtain full-text
Scottish Intercollegiate Guidelines N. Management of stable angina. Edinburgh:	Provides no relevant

Study	Reason for exclusion
SIGN, 2018.	outcomes
Sefrin P, Maier S. Study Group of the Bavarian Heart Attack Network: Preclinical standards in the treatment of heart attack. Notarzt. 2011;27(3):101-4.	Provides no relevant outcomes
Siefers R, Dunkley S, Tagney J. Developing an evidence base for core nursing standards for patients post primary Percutaneous Coronary Intervention. European Journal of Cardiovascular Nursing. 2016;15:S57.	Not a guideline, recommendation or standard
Silber S, Van De Werf F. Acute coronary syndrome with persistent ST-segment elevation (STEMI). ESC/DGK pocket guidelines. Kardiologe. 2010;4(2):93-106.	Older version of guideline, standard or recommendation
Singbal Y, Lim R. Training standards and recommendations for intervention on chronic total occlusions. Current Cardiology Reviews. 2015;11(4):328-33.	Not a guideline, recommendation or standard
Sociedad Argentina de C. Consenso de Infarto Agudo de Micardio con Elevacion del segmento ST. Resvista Argentina de Cardiologia. 2015;83(4).	Could not be accurately translated to English
Sociedad Argentina de C. Consenso para el manejo de pacientes con Síndrome Coronario Agudo sin Supradesnivel del Segmento ST (Angina Inestable e Infarto de Miocardio sin elevación del ST). Resvista Argentina de Cardiologia. 2014;82(1).	Could not be accurately translated to English
Sociedade Brasileira de C. [IV Guidelines of Sociedade Brasileira de Cardiologia for Treatment of Acute Myocardial Infarction with ST-segment elevation]. Arquivos brasileiros de cardiologia. 2009;93(6 Suppl 2):e179-264.	Older version of guideline, standard or recommendation
Sousa-Uva M, Neumann F-J, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Journal Of Cardio-Thoracic Surgery: Official Journal Of The European Association For Cardio-Thoracic Surgery. 2019;55(1):4-90.	Guideline (or other) already identified in another journal
Špmar J, Vítovec J, Hradec J, Málek I, Meluzín J, Špmarová L, et al. Czech Society of Cardiology guidelines for the diagnosis and treatment of chronic heart failure 2011. Cor et Vasa. 2012;54(2):E113-E34.	Provides no relevant outcomes
Stankovic G, Darremont O, Ferenc M, Hildick-Smith D, Louvard Y, Albiero R, et al. Percutaneous coronary intervention for bifurcation lesions: 2008 consensus document from the fourth meeting of the European Bifurcation Club. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2009;5(1):39-49.	Provides no relevant outcomes
Stankovic G, Lefevre T, Chieffo A, Hildick-Smith D, Lassen JF, Pan M, et al. Consensus from the 7th European Bifurcation Club meeting. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2013;9(1):36-45.	Provides no relevant outcomes
Steg G, James SK, Atar D, Badano LP, Blomstrom Lundqvist C, Borger MA, et al. ESC clinical practice guidelines for the management of acute myocardial infarction in patients with ST segment elevation. Revista Espanola de Cardiologia. 2013;66(1):e1-53.e46.	Older version of guideline, standard or recommendation
Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European heart journal. 2012;33(20):2569-619.	Older version of guideline, standard or recommendation
Steg PG, James SK, Gersh BJ. 2012 ESC STEMI guidelines and reperfusion therapy: Evidence-based recommendations, ensuring optimal patient management. Heart. 2013;99(16):1154-5.	Older version of guideline, standard or recommendation
StephanWindecker, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. Revista espanola de cardiologia (English ed). 2015;68(2):144.	Older version of guideline, standard or recommendation
Stone GW. Angioplasty strategies in ST-segment-elevation myocardial infarction: Part II: Intervention after fibrinolytic therapy, integrated treatment recommendations, and future directions. Circulation. 2008;118(5):552-66.	Not a guideline, recommendation or standard
Taggart DP, Boyle R, De Belder MA, Fox KAA. The 2010 ESC/EACTS guidelines on myocardial revascularisation. Heart. 2011;97(6):445-6.	Older version of guideline, standard or recommendation
Taylor J. 2012 ESC Guidelines on acute myocardial infarction (STEMI). European Heart Journal. 2012;33(20):2501-2.	Older version of guideline, standard or recommendation

Study	Reason for exclusion
Teo KK, Cohen E, Buller C, Hassan A, Carere R, Cox JL, et al. Canadian Cardiovascular Society/Canadian Association of;Interventional Cardiology/Canadian Society of Cardiac;Surgery Position Statement on Revascularization 2014;Multivessel Coronary Artery Disease. Canadian Journal of Cardiology. 2014;30(12):1482-91.	Provides no relevant outcomes
Teo KK, Cohen E, Buller C, Hassan A, Carere R, Cox JL, et al. Canadian Cardiovascular Society/Canadian Association ofInterventional Cardiology/Canadian Society of CardiacSurgery Position Statement on Revascularization-Multivessel Coronary Artery Disease. Canadian Journal of Cardiology. 2014;30(12):1482-91.	Duplicate
Timerman A. IV Guidelines of the Brazilian Society of Cardiology on the Treatment of Acute Myocardial Infarction with ST-segment Elevation, published as the second supplement of the December 2009 issue of the Brazilian Archives of Cardiology (Arq Bras Cardiol (2009) 93:6 (e179-e264)). Arquivos Brasileiros de Cardiologia. 2010;95(4):553.	Older version of guideline, standard or recommendation
Torbicki A, Kastrati A, Fuat A, Maggioni AP, Vahanian A, Budaj A, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). European Heart Journal. 2012;33(20):2569-619.	Older version of guideline, standard or recommendation
Torbicki A, Kastrati A, Vahanian A, Auricchio A, Hoes A, Merkely B, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2011;32(23):2999-3054.	Older version of guideline, standard or recommendation
Trupp RJ, Abraham WT. American College of Cardiology/American Heart Association 2009 clinical guidelines for the diagnosis and management of heart failure in adults: update and clinical implications. Polskie Archiwum Medycyny Wewnetrznej. 2009;119(7-8):436-8.	Full guideline identified
Tubaro M, Danchin N, Goldstein P, Filippatos G, Hasin Y, Heras M, et al. Pre-hospital treatment of STEMI patients. A scientific statement of the working group acute cardiac care of the European society of cardiology. Revista Espanola de Cardiologia. 2012;65(1):60-70.	Guideline (or other) already identified in another journal
Vaislic C. Consensus guidelines on coronary revascularization: The end of the controversy. Sang Thrombose Vaisseaux. 2011;23(1):18-24.	Could not obtain full-text
Valgimigli M, Patrono C, Collet J-P, Mueller C, Roffi M. Questions and answers on coronary revascularization: a companion document of the 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2015.	Duplicate
Valgimigli M, Patrono C, Collet JP, Mueller C, Roffi M. Questions and answers on coronary revascularization: A companion document of the 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2016;37(3):e8-e14.	Not a guideline, recommendation or standard
Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, et al. ESC guidelines on management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Revista española de cardiología. 2009;62(3):293, e1-47.	Older version of guideline, standard or recommendation
Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. [Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation]. Giornale italiano di cardiologia (2006). 2009;10(7):450-89.	Guideline (or other) already identified in another journal
Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. European heart journal. 2008;29(23):2909-45.	Older version of guideline, standard or recommendation
Walters DL, Cunningham C. Managing acute coronary syndromes in the prehospital and emergency setting: New guidelines from the Australian Resuscitation Council and New Zealand Resuscitation Council. EMA - Emergency Medicine Australasia. 2011;23(3):240-3.	Full guideline identified
Ward M. Proposed Recommendations for Myocardial Revascularisation. Heart, Lung	Older version of

Study	Reason for exclusion
& Circulation. 2015;24(7):635-43.	guideline, standard or recommendation
Welsford M, Nikolaou NI, Beygui F, Bossaert L, Ghaemmaghami C, Nonogi H, et al. Part 5: Acute Coronary Syndromes: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2015;132(16 Suppl 1):S146-76.	Guideline (or other) already identified in another journal
Welsh RC, MacFarlane K, Quraishi AuR. Canadian Cardiovascular Society and Canadian Institute of Health Information Public Reporting of Percutaneous Coronary Intervention Quality Indicators. Canadian Journal of Cardiology. 2018;34(12):1539-40.	Not a guideline, recommendation or standard
Werdan K, Ruß M, Buerke M, Engelmann L, Ferrari M, Friedrich I, et al. German-Austrian S3 guideline 'diagnosis, monitoring and therapy of cardiogenic shock due to myocardial infarction'. Kardiologe. 2011;5(3):166-224.	Could not be accurately translated to English
Werdan K, Ruß M, Buerke M, Engelmann L, Ferrari M, Friedrich I, et al. German-Austrian S3 guideline diaggnosis, monitoring and therapy of cardiogenic shock due to myocardial infarction. Intensiv- und Notfallbehandlung. 2011;36(2):49-130.	Guideline (or other) already identified in another journal
Werdan K. National disease management guidelines (NVL) for chronic CAD: What is new, what is particularly important? Herz. 2016;41(6):537-60.	Full guideline identified
White K, Macfarlane H, Hoffmann B, Sirvas-Brown H, Hines K, Rolley JX, et al. Consensus Statement of Standards for Interventional Cardiovascular Nursing Practice. Heart Lung and Circulation. 2018;27(5):535-51.	Provides no relevant outcomes
Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization. Giornale Italiano di Cardiologia. 2011;12(4):259-314.	Older version of guideline, standard or recommendation
Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularizationThe Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2010;31(20):2501-55.	Older version of guideline, standard or recommendation
Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2015;10(9):1024-94.	Older version of guideline, standard or recommendation
Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. Kardiologia polska. 2014;72(12):1253-379.	Older version of guideline, standard or recommendation
Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: The task force on myocardial revascularization of the European society of cardiology (ESC) and the European association for cardio-thoracic surgery (EACTS): Developed with the special contribution of the European association of percutaneous cardiovascular interventions (EAPCI). Russian Journal of Cardiology. 2015;118(2):5-81.	Older version of guideline, standard or recommendation
Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European heart journal. 2014;35(37):2541-619.	Older version of guideline, standard or recommendation
Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. Clinical practice guidelines of the ESC on myocardial revascularization, 2014. Revista Espanola de Cardiologia. 2015;68(2):144.e-.e.	Older version of guideline, standard or recommendation
Windecker S, Neumann F-J, Jüni P, Sousa-Uva M, Falk V. Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization. European Heart Journal. 2019;40(2):204-12.	Not a guideline, recommendation or standard
Winjns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization. Revista Portuguesa de Cardiologia. 2010;29(9):1441-2.	Could not obtain full-text
Wong GC, van Diepen S, Ainsworth C, Arora RC, Diodati JG, Liszkowski M, et al.	Provides no relevant

Study	Reason for exclusion
Canadian Cardiovascular Society/Canadian Cardiovascular Critical Care Society/Canadian Association of Interventional Cardiology Position Statement on the Optimal Care of the Postarrest Patient. Canadian Journal of Cardiology. 2017;33(1):1-16.	outcomes
Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, Jr., Ettinger SM, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. Journal Of The American College Of Cardiology. 2011;57(19):e215-e367.	Older version of guideline, standard or recommendation
Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, Jr., Ettinger SM, et al. 2011 ACCF/AHA focused update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (updating the 2007 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal Of The American College Of Cardiology. 2011;57(19):1920-59.	Older version of guideline, standard or recommendation
Wright RS, Anderson JL, Adams CD, Bridges CR, Casey Jr DE, Ettinger SM, et al. 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (Updating the 2007 Guideline): A report of the American College of cardiology foundation/American heart association task force on practice guidelines. Circulation. 2011;123(18):2022-60.	Older version of guideline, standard or recommendation
Wright RS, Anderson JL, Adams CD, Bridges CR, Casey Jr DE, Ettinger SM, et al. Erratum: 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (Updating the 2007 Guideline): A report of the American college of cardiology foundation/American heart association task force on practice guidelines (Journal of the American College of Cardiology (2011) 57 (1920-1959)). Journal of the American College of Cardiology. 2011;57(19):1960.	Older version of guideline, standard or recommendation
Wright RS, Anderson JL, Adams CD. Erratum: 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction (Updating the 2007 guideline): A report of the American college of cardiology foundation/American heart association task force on practice guidelines (Journal of the American College of Cardiology (2011) 57 (1920-1959)). Journal of the American College of Cardiology. 2011;58(9):993-4.	Older version of guideline, standard or recommendation
Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: Executive summary: A report of the American college of cardiology foundation/American Heart Association task force on practice guidelines. Circulation. 2013;128(16):1810-52.	Not relevant to PCI
Yavelov SI, Ruda YM, Averkov VO, Panchenko PE. [Recommendations of the Society of Specialists in Urgent Cardiology Diagnosis and Treatment of Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. Part 1]. Kardiologiia. 2017;57(8):80-100.	Could not obtain full-text
Zijlstra F, Van Geuns RJ. Revised NHG practice guideline 'Acute coronary syndrome': A strong link in the chain of treatment. Nederlands Tijdschrift voor Geneeskunde. 2013;157(9).	Not a guideline, recommendation or standard
Zuin G, Parato VM, Groff P, Gulizia MM, Di Lenarda A, Cassin M, et al. [ANMCO/SIMEU Consensus document: In-hospital management of patients presenting with chest pain]. Giornale italiano di cardiologia (2006). 2016;17(6):416-46.	Not relevant to PCI
Chinese guideline for percutaneous coronary intervention(2016). Zhonghua Xin Xue Guan Bing Za Zhi. 2016;44(5):382-400.	Could not obtain full-text
Chinese guideline for percutaneous coronary intervention(pocket guideline). Zhonghua xin xue guan bing za zhi. 2012;40(4):271-7.	Older version of guideline, standard or recommendation
Current care guidelines: STEMI-treatment. Duodecim; lääketieteellinen	Not a guideline,

Study	Reason for exclusion
aikakauskirja. 2011;127(18):1946-7.	recommendation or standard
2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(23):e663-828.	Older version of guideline, standard or recommendation
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in Collaboration With the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheterization and Cardiovascular Interventions. 2013;45(4).	Older version of guideline, standard or recommendation
2018 ESC/EACTS Guidelines on Myocardial Revascularization. Revista Espanola de Cardiologia. 2019;72(1):73.e1-.e6.	Guideline (or other) already identified in another journal
ACCF/AHA/SCAI 2013 Update of the Clinical Competence Statement on Coronary Artery Interventional Procedures: A Report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training (Writing Committee to Revise the 2007 Clinical Competence Statement on Cardiac Interventional Procedures). Catheterization and Cardiovascular Interventions. 2013;82(2):E69-E111.	Guideline (or other) already identified in another journal
Acute coronary syndromes: Introduction to acute coronary syndromes. ARC and NZRC guideline 2011. EMA - Emergency Medicine Australasia. 2011;23(3):299-301.	Older version of guideline, standard or recommendation
Acute coronary syndromes: Presentation with ACS. ARC and NZRC guideline 2011. EMA - Emergency Medicine Australasia. 2011;23(3):302-7.	Not relevant to PCI
Acute coronary syndromes: Reperfusion strategy. ARC and NZRC guideline 2011. EMA - Emergency Medicine Australasia. 2011;23(3):312-6.	Older version of guideline, standard or recommendation
Correction: 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with st-elevation myocardial infarction: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/ aha guideline for the management of st-elevation myocardial infarction. Circulation. 2016;133(11):e442-e3.	Not a guideline, recommendation or standard
Corrigendum to: 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2018;39(21):1991.	Provides no relevant outcomes
Erratum to Brazilian society of cardiology guidelines on unstable angina and non-st-segment elevation myocardial infarction (2nd edition, 2007) - 2013 updating (Arq Bras Cardiol, (2014) 102, 3 Supl.1, 1-61). Arquivos Brasileiros de Cardiologia. 2014;103(5):443.	Not relevant to PCI
Erratum to: Guidelines of the Brazilian society of cardiology for professional and institutional quality, center for training and professional certification in hemodynamics and interventional cardiology (Edition III - 2013) (Arquivos Brasileiros de cardiologia, (2013), 101, 6, SUPPL. 4, (1-58)). Arquivos Brasileiros de Cardiologia. 2014;102(4):415.	Older version of guideline, standard or recommendation
Erratum: 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/Non-ST-elevation myocardial infarction: A report of the American college of cardiology foundation/American heart association task force on practice guidelines (Circulation (2011) 123 (e426-e579)). Circulation. 2011;123(22):e627.	Older version of guideline, standard or recommendation
Erratum: 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (Updating the 2007 Guideline): A report of the american college of cardiology foundation/american heart association task force on practice guidelines (Circulation (2011) 123 (2022-2060)). Circulation. 2011;124(12):e337-e40.	Older version of guideline, standard or recommendation
Erratum: 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable Angina/Non-ST-Elevation myocardial infarction: A report of the american college of cardiology	Older version of guideline, standard or recommendation

Study	Reason for exclusion
foundation/American heart association task force on practice guidelines (Circulation (2013) 127 (e663-e828)). Circulation. 2013;127(24):e863-e4.	
Erratum: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A Report of the american college of cardiology foundation/American heart association task force on practice guidelines (Circulation (2013) 127 (e362-e425)). Circulation. 2013;128(25):e481.	Older version of guideline, standard or recommendation
Erratum: 2014 ACC/AHA guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Circulation (2014) 130 (e344-e426)). Circulation. 2014;130(25):e433-e4.	Guideline (or other) already identified in another journal
Erratum: 2014 ACC/AHA guideline for the management of patients with nonST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. (J Am Coll Cardiol (2014) 64(e139228)). Journal of the American College of Cardiology. 2014;64(24):2713-4.	Provides no relevant outcomes
Erratum: 2014 ACC/AHA guideline for the management of patients with nonST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Executive summary (J Am Coll Cardiol (2014) 64 (264587)). Journal of the American College of Cardiology. 2014;64(24):2714-5.	Not relevant to PCI
Erratum: 2014 ACC/AHA guideline for the management of patients with Non-ST-elevation acute coronary syndromes: Executive summary: A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Circulation (2014) 130 (2354-2394)). Circulation. 2014;130(25):e431-e2.	Guideline (or other) already identified in another journal
Erratum: Part 10: Acute coronary syndromes: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care (Circulation (2010) 122 (S787-S817)). Circulation. 2012;125(2):e265.	Older version of guideline, standard or recommendation
Erratum: Part 10: Acute coronary syndromes: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care (Circulation (2010) 122: SUPPL. 3 (S787-S817)). Circulation. 2011;123(6):e238.	Older version of guideline, standard or recommendation
Erratum: ST-elevation myocardial infarction: New Zealand management guidelines (New Zealand Medical Journal (2005) vol. 118 (1223)). New Zealand Medical Journal. 2008;121(1275).	Published before 2008
Guideline and consensus for the management of patients with non-ST-elevation acute coronary syndrome(2016). Zhonghua xin xue guan bing za zhi. 2017;45(5):359-76.	Could not obtain full-text
Guideline of non-ST segment elevation acute coronary syndrome. Chinese Journal of Cardiology. 2012;40(5):353-67.	Could not obtain full-text
Guideline on the diagnosis and therapy of ST-segment elevation myocardial infarction. Zhonghua xin xue guan bing za zhi. 2015;43(5):380-93.	Could not obtain full-text
Guidelines for Diagnosis and Management of Acute Coronary Syndrome. ED Management. 2009:4.	Could not obtain full-text
Guidelines for percutaneous coronary intervention (2009). Zhonghua xin xue guan bing za zhi [Chinese journal of cardiovascular diseases]. 2009;37(1):4-25.	Older version of guideline, standard or recommendation
Guidelines of the Brazilian Society of Cardiology for unstable angina and Non-ST segment elevation acute myocardial infarction. International Journal of Atherosclerosis. 2008;3(2):58-86.	Older version of guideline, standard or recommendation
SIGN updates guideline on stable angina. Guidelines in Practice. 2018;21(5):6.	Not a guideline, recommendation or standard
Stable angina guidelines. Nursing & Residential Care. 2016;18(10):521.	Not a guideline, recommendation or standard
The 4th Guidelines on the Treatment of Acute ST-segment Elevation Myocardial Infarction of the Brazilian Society of Cardiology. Arquivos Brasileiros de Cardiologia. 2009;93(6 SUPPL. 2):e179-e264.	Older version of guideline, standard or recommendation

Table A.24: Table of studies excluded after full-text review (RQ3)

Study	Reason for exclusion
Abrams J. Physician experience vs. hospital volume in primary PCI...percutaneous coronary intervention. Clinical Cardiology Alert. 2009;28(4):31-2.	Not primary research
Acharya T, Kennedy K, Spertus JA, Kennedy KF, Reddy HKK, Bhullar A, et al. Percutaneous coronary intervention outcomes in america's safety net-a study of NCDR. Catheterization and Cardiovascular Interventions. 2016;87:S118-S9.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Acharya T, Salisbury AC, Spertus JA, Kennedy KF, Bhullar A, Reddy HKK, et al. In-Hospital Outcomes of Percutaneous Coronary Intervention in America's Safety Net: Insights From the NCDR Cath-PCI Registry. JACC: Cardiovascular Interventions. 2017;10(15):1475-85.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Akin I, Hochadel M, Schneider S, Abdel-Wahab M, Zahn R, Senges J, et al. Volume-outcomes relationship in the Era of modern coronary intervention - Results from the prospective multicenter German DES.DE Registry. Catheterization and Cardiovascular Interventions. 2013;82(6):E788-E97.	Does not report adjusted rates.
Allareddy V, Ward MM, Allareddy V, Konety BR. Effect of meeting leapfrog volume thresholds on complication rates following complex surgical procedures. Ann Surg. 2010;251(2):377-83.	Same dataset as one already included
Amato L, Fusco D, Acampora A, Bontempi K, Rosa AC, Colais P, et al. Volume and health outcomes: evidence from systematic reviews and from evaluation of Italian hospital data. Epidemiol Prev. 2017;41(5-6 (Suppl 2)):1-128.	Procedural volumes not defined categorically
Anis A, Normand SLT, Wolf RE, Lovett A, Mauri L, Patel N, et al. Primary percutaneous coronary intervention with or without cardiac surgery on-site: Massachusetts' experience. Circulation. 2010;120(21):2154.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Arora S, Patel N, Patel N, Bhalara V, Chothani A, Savani G, et al. Variability in drug eluting stent use: Influence of operator volume and institutional volume. Catheterization and Cardiovascular Interventions. 2014;83:S189-S90.	Does not report mortality or survival
Badheka AO, Panaich SS, Arora S, Patel N, Patel NJ, Savani C, et al. Percutaneous Coronary Intervention: Relationship Between Procedural Volume and Outcomes. Curr Cardiol Rep. 2016;18(4).	Not primary research
Badheka AO, Patel NJ, Grover P, Singh V, Patel N, Arora S, et al. Response to Letter Regarding Article 'Impact of Annual Operator and Institutional Volume on Percutaneous Coronary Intervention Outcomes: A 5-Year United States Experience (2005-2009)'. Circulation. 2015;132(5):e36-7.	Not primary research
Bagai A, Rezaei E, Al-Nasser S, Al Lawati H, Finken L, Cheema A. The learning curve for transradial primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Catheterization and Cardiovascular Interventions. 2015;85:S168.	Does not report mortality or survival
Baig SS, Altman DG, Taggart DP. Major geographical variations in elective coronary revascularization by stents or surgery in England. European Journal of Cardio-thoracic Surgery. 2015;47(5):855-9.	Does not report mortality or survival
Ball WT, Sharieff W, Jolly SS, Hong T, Kutryk MJ, Graham JJ, et al. Characterization of operator learning curve for transradial coronary interventions. Circ Cardiovasc Interv. 2011;4(4):336-41.	Does not report mortality or survival
Baron SJ, Yeh RW, Cohen DJ. The challenges of success: maintaining access to high-quality percutaneous coronary intervention in the face of declining procedural volumes. Circulation. 2014;130(16):1343-5.	Not primary research
Basavarajaiah S, Gajendragadkar P, Brown A, McCormick L. Switching from femoral to radial access for percutaneous coronary intervention: Should technical difficulties deter would-be converts? J Am Coll Cardiol. 2012;59(13):E1523.	Does not report mortality or survival
Bosson N, Fang A, Kaji AH, Thomas JL, Gausche-Hill M, Niemann JT. Treatment at high-volume cardiac arrest centers is associated with better neurologic outcome after out-of-hospital cardiac arrest. Ann Emerg Med. 2016;68(4):S109.	Subject not PCI
Brilakis ES, Banerjee S, Karmpaliotis D, Lombardi WL, Tsai TT, Shunk KA, et al.	Does not report mortality

Study	Reason for exclusion
Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). JACC: Cardiovascular Interventions. 2015;8(2):245-53.	or survival
Brindis RG, Dehmer GJ. The Volume–Outcome Relationship Revisited: Does It Matter for High-Risk PCI? : JACC: Cardiovascular Interventions; 2016.	Not primary research
Brogan R, Simms AD, Batin PD, Timmis A, Gale CP. Association between hospital characteristics, missed care opportunities and mortality in patients with STEMI. A cohort study on behalf of NICOR. Eur Heart J. 2014;35:469.	Conference paper or abstract
Callaway CW, Schmicker RH, Brown SP, Albrich JM, Andrusiek DL, Aufderheide TP, et al. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. Resuscitation. 2014;85(5):657-63.	Subject not PCI
Canadian Institute for Health I. Cardiac Care Quality Indicators Report. 2017.	Does not report adjusted rates
Capodanno D, Buccheri S. Operator volume and mortality in percutaneous coronary intervention: A call for better competency metrics. Eur Heart J. 2018;39(18):1635-7.	Not primary research
Chamnarnphol N, Wisaratapong T, Cheevatanakornkul S. Correlation between percutaneous coronary intervention volume, door-to-balloon time and mortality of patients with acute ST-segment elevation myocardial infarction. Journal of the Medical Association of Thailand. 2012;95(3):325-9.	Single centre study
Chen J, Krumholz HM, Wang Y, Curtis JP, Rathore SS, Ross JS, et al. Differences in patient survival after acute myocardial infarction by hospital capability of performing percutaneous coronary intervention: Implications for regionalization. Arch Intern Med. 2010;170(5):433-9.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Chin KL, Tacey M, Reid CM, Tonkin A, Hopper I, Brennan A, et al. Temporal Changes in Characteristics, Treatment and Outcomes of Heart Failure Patients Undergoing Percutaneous Coronary Intervention Findings from Melbourne Interventional Group Registry. Heart Lung and Circulation. 2018.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Choi YJ, Kim JB, Cho SJ, Cho J, Sohn J, Cho SK, et al. Changes in the practice of coronary revascularization between 2006 and 2010 in the Republic of Korea. Yonsei Med J. 2015;56(4):895-903.	Procedural volumes not defined categorically
Chou Y-Y, Tu Y-K, Tung Y-C. The relationship between physician and hospital PCI volume thresholds and mortality. Taiwan Gong Gong Wei Sheng Za Zhi. 2017;36(2):174.	Same dataset as an included study
Chung SC, Sundstrom J, Gale CP, James S, Deanfield J, Wallentin L, et al. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. Bmj. 2015;351:h3913.	Subject not PCI
Couper K, Kimani PK, Gale CP, Quinn T, Squire IB, Marshall A, et al. Variation in outcome of hospitalised patients with out-of-hospital cardiac arrest from acute coronary syndrome: a cohort study. Health Services and Delivery Research. 2018.	Subject not PCI
Dakik HA, Karowni W, El-Sibai K, Kobrossi S, Abdul-Ameer K, Tamim H. The Impact of Formal Training and Certification on the Relationship between Volume and Outcomes in Percutaneous Coronary Interventions. Crit Pathw Cardiol. 2018;17(3):155-60.	Single Operator Study
Damiani G, Marchetti M, Di Bidino R, Sammarco A, Facco R, Cambieri A, et al. [The use of procedures volume indicators in an Italian Teaching Hospital]. Ann Ig. 2008;20(3):223-32.	Single centre study
Dehmer GJ, Holper EM. Does Practice Make Perfect? : JACC: Cardiovascular Interventions; 2017.	Not primary research
Dimick JB, Staiger DO, Osborne NH, Nicholas LH, Birkmeyer JD. Composite measures for rating hospital quality with major surgery. Health Serv Res. 2012;47(5):1861-79.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Doll JA, Dai D, Roe MT, Messenger JC, Sherwood MW, Prasad A, et al. Assessment of Operator Variability in Risk-Standardized Mortality Following	Procedural volumes not defined categorically

Study	Reason for exclusion
Percutaneous Coronary Intervention: A Report From the NCDR. JACC: Cardiovascular Interventions. 2017;10(7):672-82.	
Dong A, Malik A, Allenback G, Diep J, Ahsan C. Impact of hospital procedure volumes on outcomes of PCI for ST-segment elevation myocardial infarction in the United States. J Am Coll Cardiol. 2018;71(11).	Conference paper or abstract
Dooley DJ, Kern M, Haryani A, Gonzalez MA, Torguson R, Waksman R, et al. Operator volumes and salvage index in AMI. Journal of Cardiovascular Magnetic Resonance. 2012;14.	Conference paper or abstracts
Fanaroff AC, Zakroysky P, Wojdyla D, Sherwood MW, Roe MT, Wang TY, et al. Association between operator pci volume and long-term outcomes in older adults: A report from the NCDR CathPCI registry. Circulation. 2017;136.	Conference paper or abstract
Fentanes E, Wisenbaugh TW. Ten years of percutaneous coronary intervention in a low-volume military treatment facility: a quality improvement project. Mil Med. 2013;178(9):1029-35.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Furuya J, Muto M, Yamane M, Muramatsu T, Okamura A, Igarashi Y, et al. Procedure outcomes of lower volume centres in percutaneous coronary intervention for chronic total occlusions: Sub-analysis from Japanese multicentre registry data. EuroIntervention. 2015.	Does not report mortality or survival
Galassi AR, Sianos G, Reifart N, Castaing M, Escaned J, Marza F, et al. Retrograde recanalization of chronic total occlusions in Europe: Procedural and in-hospital outcomes from the multicenter ercto registry. JACC: Cardiovascular Interventions. 2014;7(2):S19.	Does not report mortality or survival
Ghaferi AA, Osborne NH, Dimick JB. Does Voluntary Reporting Bias Hospital Quality Rankings? Journal of Surgical Research. 2010;161(2):190-4.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Gilchrist IC. The transradial learning curve and volume-outcome relationship. Interv Cardiol Clin. 2015;4(2):203-11.	Not primary research
Gutierrez A, Tsai TT, Stanislawski MA, Vidovich M, Bryson CL, Bhatt DL, et al. Adoption of transradial percutaneous coronary intervention and outcomes according to center radial volume in the veterans affairs healthcare system: Insights from the veterans affairs clinical assessment, reporting, and tracking (CART) program. Circulation: Cardiovascular Interventions. 2013;6(4):336-46.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Habara M, Tsuchikane E, Muramatsu T, Kashima Y, Okamura A, Mutoh M, et al. Comparison of percutaneous coronary intervention for chronic total occlusion outcome according to operator experience from the Japanese retrograde summit registry. Catheterization and Cardiovascular Interventions. 2016;87(6):1027-35.	Does not report mortality or survival
Hannan EL, Zhong Y, Jacobs AK, Ling FSK, Berger PB, Walford G, et al. Incomplete revascularization for percutaneous coronary interventions: Variation among operators, and association with operator and hospital characteristics. Am Heart J. 2017;186:118-26.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Hannan EL, Zhong Y, Jacobs AK, Stamato NJ, Berger PB, Walford G, et al. Patients with chronic total occlusions undergoing percutaneous coronary interventions. Circulation: Cardiovascular Interventions. 2016;9(5).	Relationship between hospital or operator volume and PCI outcomes is not investigated
Harrison RW, Simon D, Miller AL, De Lemos JA, Peterson ED, Wang TY. Association of hospital myocardial infarction volume with adherence to American College of Cardiology/American Heart Association performance measures: Insights from the National Cardiovascular Data Registry. Am Heart J. 2016;178:95-101.	Subject not PCI
Hess CN, Peterson ED, Neely ML, Dai D, Hillegass WB, Krucoff MW, et al. The learning curve for transradial percutaneous coronary intervention among operators in the United States: a study from the National Cardiovascular Data Registry. Circulation. 2014;129(22):2277-86.	Does not report adjusted rates
Hlatky MA. Volume, outcome, and policy. Journal of Interventional Cardiac Electrophysiology. 2013;36(2):151-5.	Not primary research

Study	Reason for exclusion
Ho V, Ku-Goto MH, Jollis JG. Certificate of need (CON) for cardiac care: Controversy over the contributions of CON. Health Serv Res. 2009;44(2P1):483-500.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Howard DH, Shen YC. Trends in PCI volume after negative results from the COURAGE trial. Health Serv Res. 2014;49(1):153-70.	Does not report mortality or survival
Hulme W, Sperrin M, Rushton H, Ludman PF, De Belder M, Curzen N, et al. Is there a relationship of operator and center volume with access site-related outcomes? Circulation: Cardiovascular Interventions. 2016;9(5).	Relationship between hospital or operator volume and PCI outcomes is not investigated
Iqbal MB, Arujuna A, Ilsley C, Archbold A, Crake T, Firoozi S, et al. Radial versus femoral access is associated with reduced complications and mortality in patients with non-ST-segment-elevation myocardial infarction: An observational cohort study of 10 095 patients. Circulation: Cardiovascular Interventions. 2014;7(4):456-64.	Procedural volumes not defined categorically
Isogai T, Yasunaga H, Matsui H, Tanaka H, Fushimi K. Relationship between hospital volume and major cardiac complications of rotational atherectomy: A nationwide retrospective cohort study in Japan. J Cardiol. 2016;67(5):442-8.	Does not report mortality or survival
Jain KJ, Aditya R, Krishna LSR, Sai Satish O. Outcome of primary angioplasty in high volume tertiary care centre. Indian Heart J. 2014;66:S24.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Jollis JG. The New York State Primary Angioplasty Registry and Procedural Volume. J Am Coll Cardiol. 2009;53(7):580-1.	Not primary research
Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. The Lancet. 2011;377(9775):1409-20.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Jolly SS, Cairns J, Yusuf S, Niemela K, Steg PG, Worthley M, et al. Procedural volume and outcomes with radial or femoral access for coronary angiography and intervention. J Am Coll Cardiol. 2014;63(10):954-63.	Procedural volumes not defined categorically
Kenney KM, Marzo MC, Ondrasik NR, Wisenbaugh T. Percutaneous coronary intervention outcomes in a low-volume center: Survival, stent thrombosis, and repeat revascularization. Circulation: Cardiovascular Quality and Outcomes. 2009;2(6):671-7.	Single centre study
Kern M. What is the Annual Volume Requirement for a PCI Operator? 2017.	Not primary research
Khatana SA, Groeneveld P, Giri JS. Association between new york state hospital post-percutaneous coronary intervention mortality and readmissions and CMS hospital star ratings. J Am Coll Cardiol. 2018;71(11).	Relationship between hospital or operator volume and PCI outcomes is not investigated;
Khatana SAM, Fiorilli PN, Groeneveld PW, Giri JS. Association between percutaneous coronary intervention outcomes and physician education and board certification in New York state 2010-2012. Circulation: Cardiovascular Quality and Outcomes. 2017;10.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Khatana SAM, Fiorilli PN, Nathan AS, Kolansky DM, Mitra N, Groeneveld PW, et al. Association Between 30-Day Mortality After Percutaneous Coronary Intervention and Education and Certification Variables for New York State Interventional Cardiologists. Circ Cardiovasc Interv. 2018;11(9):e006094.	Same dataset as an included study
Khattab AA, Hamm CW, Senges J, Toelg R, Geist V, Bonzel T, et al. Sirolimus-eluting stent treatment at high-volume centers confers lower mortality at 6-month follow-up: results from the prospective multicenter German Cypher Registry. Circulation. 2009;120(7):600-6.	Does not report adjusted rates
Khera R, Cram P, Girotra S. Letter by Khera et al Regarding Article, 'Impact of Annual Operator and Institutional Volume on Percutaneous Coronary Intervention Outcomes: A 5-Year United States Experience (2005-2009)'.	Not primary research

Study	Reason for exclusion
Circulation. 2015;132(5):e35-e.	
Kim JH, Lee Y, Park EC. Beyond volume: Hospital-based healthcare technology as a predictor of mortality for cardiovascular patients in Korea. Medicine (United States). 2016;95(24).	Conference paper or abstract
Kim JH, Kim JM, Park EC. The Association of Hospital Volume of Percutaneous Coronary Intervention with Cardiac Mortality. Health Policy and Management. 2018;28(2):168-77.	Procedural volumes not defined categorically
Kim MK, Kim W, Ha SJ, Yu TK, Woo JS, Kim SJ, et al. Clinical outcomes of primary percutaneous coronary interventions for acute myocardial infarctions in hospitals with and without onsite cardiac surgery backup. American Journal of Cardiology. 2011;107(8):6A.	Conference paper or abstract
Kim YH, Her AY. Relationship between coronary angioplasty laboratory volume and short-term outcome after hospital discharge. Eur Heart J. 2011;32:223-4.	Subject not PCI
Kodaira M. Differences of in-hospital outcomes within patients undergoing percutaneous coronary intervention at institutions with high versus low procedural volume. Circulation. 2017;136.	Conference paper or abstract
Koshida R, Okamura A, Muramatsu T, Fujita T, Muto M, Oida A, et al. Difference of procedure outcomes between higher and lower volume operators in percutaneous coronary intervention for chronic total occlusions: Subanalysis from japanese multicenter registry data. J Am Coll Cardiol. 2014;63(12):A1619.	Conference paper or abstract
Kugelmass A, Brown PP, Cohen DJ, Reynolds MR, Culler SD, Simon AW. Comparing hospital ranking for nonemergent PCI and CABG: How many hospitals can perform both procedures above average and does it matter? Circulation: Cardiovascular Quality and Outcomes. 2011;4(6).	Relationship between hospital or operator volume and PCI outcomes is not investigated
Kugelmass AD, Brown PP, Cohen DJ, Reynolds MR, Culler SD, Simon AW. PCI outcomes among medicare beneficiaries during fiscal year 2010 at hospitals with and without cardiac surgery on-site. Circulation. 2012;126(21).	Relationship between hospital or operator volume and PCI outcomes is not investigated
Kumbhani DJ, Bittl JA. Much Ado About Nothing?: The Relationship of Institutional Percutaneous Coronary Intervention Volume to Mortality. Am Heart Assoc; 2017.	Not primary research
Langabeer JR, Kim J, Helton J. Exploring the Relationship Between Volume and Outcomes in Hospital Cardiovascular Care. Qual Manag Health Care. 2017;26(3):160-4.	Same dataset as an included study
Langabeer JR, Helton J, Kim J, Fowler R. Reassessing the impact of hospital PCI volume on STEMI outcomes. Circulation: Cardiovascular Quality and Outcomes. 2017;10.	Conference paper or abstract
Lawson WE, Wilbert LA, Gumersell K, Horbatuk E, Leonard T, Dorney A, et al. Practice process variability and outcomes, relation to interventionalist volume. Circulation: Cardiovascular Quality and Outcomes. 2017;10.	Does not report adjusted rates
Lim KS, Woo JS, Hong KH, Kang WY, Lim SY, Ahn YK, et al. Effect of volume of percutaneous coronary intervention on clinical outcomes in patients with acute myocardial infarctions in hospitals with and without on-site cardiac surgery backup. Int J Cardiol. 2013;163(2):216-7.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Lin HC, Lee HC, Chu CH. The volume-outcome relationship of percutaneous coronary intervention: Can current procedure volume minimums be applied to a developing country? Am Heart J. 2008;155(3):547-52.	Same dataset as an included study
Liu CY, Lin YN, Lin CL, Chang YJ, Hsu YH, Tsai WC, et al. Cardiologist service volume, percutaneous coronary intervention and hospital level in relation to medical costs and mortality in patients with acute myocardial infarction: a nationwide study. Qjm. 2014;107(7):557-64.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Lu TH, Li ST, Liang FW, Lee JC, Yin WH. When high-volume PCI operators in high-volume hospitals move to lower volume hospitals—Do they still maintain high volume and quality of outcomes? Catheterization and Cardiovascular Interventions. 2018;92(4):644-50.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Lui CG, Malik AO, Allenback GL, Diep J, Ahsan CH. Access to PPCI is a	Does not report adjusted

Study	Reason for exclusion
determinant of survival of patients with ST segment elevated myocardial infarction in the state of Nevada. Global Heart. 2016;11(2):e150.	rates.
Machino TO, Toyama M, Obara K, Takeyasu N, Watanabe S, Aonuma K. Effect of hospital case volume on treatment and in-hospital outcomes in patients undergoing percutaneous coronary intervention for acute myocardial infarction: Results from the Ibaraki Coronary Artery Disease Study (ICAS) registry. Int Heart J. 2008;49(3):249-60.	Does not report adjusted rates
Madan M, Nikhil J, Hellkamp AS, Pieper KS, Labinaz M, Cohen EA, et al. Effect of operator and institutional volume on clinical outcomes after percutaneous coronary interventions performed in Canada and the United States: A brief report from the Enhanced Suppression of the Platelet glycoprotein IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) study. Canadian Journal of Cardiology. 2009;25(8):e269-e72.	Does not report mortality or survival
Malik AO, Abela O, Allenback G, Devabhaktuni S, Lui C, Singh A, et al. ST-segment elevation myocardial infarction, systems of care. An urgent need for policies to co-ordinate care in order to decrease in-hospital mortality. Int J Cardiol. 2017;240:82-6.	Does not report adjusted rates;
Maynard C, Rao SV, Gregg M, Phillips RC, Reisman M, Tucker E, et al. The role of out-of-hospital cardiac arrest in predicting hospital mortality for percutaneous coronary interventions in the Clinical Outcomes Assessment Program. J Invasive Cardiol. 2009;21(1):1-5.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Milliken JC, Rudersdorf PD, Carey JS, Danielsen B. Cause and effects of decreasing coronary revascularization procedures in California hospitals, 2006 to 2010. American Journal of Cardiology. 2014;113(3):465-70.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Minges KE, Wang Y, Dodson JA, Normand SLT, Rathore SS, Ting HH, et al. Physician annual volume and in-hospital mortality following percutaneous coronary intervention. Circulation. 2011;124(21).	Conference paper or abstract
Miyachi H, Takagi A, Miyauchi K, Yamasaki M, Yamashita J, Suzuki M, et al. The volume of percutaneous coronary intervention procedures did not associate with in-hospital mortality for ST-segment elevation myocardial infarction in our metropolitan area. Eur Heart J. 2014;35:819-20.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Nagaraja V, Nolan J, Mamas MA. Radial access: operator experience and center volume. Card Interv Today. 2016;10:35.	Not primary research
Nicholas LH, Iwashyna TJ, Dimick JB. Quality measures for assessing hospital mortality: Evaluation using instrumental variable analysis. Journal of Surgical Research. 2012;172(2):211.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Olcay A. Hospital volume and mortality relation in PCI - Is there a need for modification of ACC/AHA percutaneous coronary intervention guidelines in Asia? Anatolian Journal of Cardiology / Anadolu Kardiyoloji Dergisi. 2013;13(3):243-4.	Not primary research
O'Neill WW. A Case Against Low-Volume Percutaneous Coronary Intervention Centers. Circulation. 2009;120(7):546-8.	Not primary research
Onwordi E, Alaour B, Dana A. Clinical outcomes of chronic total occlusion percutaneous coronary intervention-a 5 year experience in a non-surgical centre. J Am Coll Cardiol. 2017;70(18):B250.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Park S, Sasaki N, Morishima T, Ikai H, Imanaka Y. The number of cardiologists, case volume, and in-hospital mortality in acute myocardial infarction patients. Int J Cardiol. 2013;168(4):4470-1.	Subject not PCI
Patel N, Arora S, Patel N, Grover P, Chothani A, Badheka A, et al. Impact of annual operator volume on percutaneous coronary intervention outcomes in high risk subgroups in the united states: A five year contemporary experience (2005 to 2009). Catheterization and Cardiovascular Interventions. 2014;83:S175-S7.	Conference paper or abstract
Piegas LS, Haddad N. Percutaneous coronary intervention in Brazil. Results from the Brazilian Public Health System. Arq Bras Cardiol. 2011;96(4):317-24.	Does not report adjusted rates

Study	Reason for exclusion
Rahman M, Bangash A, Nfor T, Ahmed M, Pienkos P, Museitif R, et al. Fluoroscopic time during percutaneous coronary intervention is associated with higher morbidity and mortality regardless of operator volume and ACC/AHA lesion severity. Catheterization and Cardiovascular Interventions. 2010;75:S73-S4.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Ross JS, Normand S-LT, Wang Y, Ko DT, Chen J, Drye EE, et al. Hospital volume and 30-day mortality for three common medical conditions. New England Journal of Medicine. 2010;362(12):1110-8.	Subject not PCI
Sakakura K, Inohara T, Kohsaka S, Amano T, Uemura S, Ishii H, et al. Incidence and Determinants of Complications in Rotational Atherectomy: Insights from the National Clinical Data (J-PCI Registry). Circulation: Cardiovascular Interventions. 2016;9(11).	Does not report mortality or survival
Sethi A, Singbal Y, Kodumuri V, Prasad V. Inpatient mortality and its predictors after pericardiocentesis: An analysis from the Nationwide Inpatient Sample 2009–2013. J Interv Cardiol. 2018;31(6):815-25.	Subject not PCI
Seto A, Kern MJ. Declining pci volume: Does low volume mean low quality? Catheterization and Cardiovascular Interventions. 2013;81(1):40-1.	Not primary research
Shaefi S, O'Gara B, Kociol RD, Joynt K, Mueller A, Nizamuddin J, et al. Effect of cardiogenic shock hospital volume on mortality in patients with cardiogenic shock. J Am Heart Assoc. 2015;4(1):1-N.PAG.	Subject not PCI
Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Hong MK, et al. The relationship between hospital volumes and mortality rates after acute myocardial infarction. J Am Coll Cardiol. 2012;59(13):E381.	Subject not PCI
Shlofmitz E, Doshi R, Shlofmitz R, Lee M. Impact of high operator volume on mortality with contemporary PCI. J Am Coll Cardiol. 2017;70(18):B249.	Conference paper or abstract
Singh V, Patel J, Patel N, Patel N, Arora S, Patel N, et al. Effect of intravascular ultrasound guided percutaneous coronary interventions on in-hospital outcomes. J Am Coll Cardiol. 2015;65(10):A1686.	Conference paper or abstract
Thompson CA, Jayne JE, Robb JF, Friedman BJ, Kaplan AV, Hettleman BD, et al. Retrograde Techniques and the Impact of Operator Volume on Percutaneous Intervention for Coronary Chronic Total Occlusions. An Early U.S. Experience. JACC: Cardiovascular Interventions. 2009;2(9):834-42.	Does not report mortality or survival
Tomasello SD, Sianos G, Werner G, Escaned J, Boukris M, Gagnor A, et al. Retrograde recanalization of chronic total occlusions in europe: Procedural and in-hospital outcomes from the multicenter ercto registry. G Ital Cardiol. 2014;15:e32-e3.	Conference paper or abstract
Tung YC, Chang GM, Chien KL, Tu YK. The relationships among physician and hospital volume, processes, and outcomes of care for acute myocardial infarction. Med Care. 2014;52(6):519-27.	Relationship between hospital or operator volume and PCI outcomes is not investigated
Wang TY, Grines C, Ortega R, Dai D, Jacobs AK, Skelding KA, et al. Women in interventional cardiology: Update in percutaneous coronary intervention practice patterns and outcomes of female operators from the National Cardiovascular Data Registry®. Catheterization and Cardiovascular Interventions. 2016;87(4):663-8.	Same dataset as an included study
Wei J, Messenger J, Curtis JP, Chang LC. A hospital outcome prediction model in percutaneous coronary intervention: Volume-specific analysis based on adverse ratios and risk adjusted mortality. Circulation. 2012;126(21).	Conference paper or abstract
West RM, Cattle BA, Bouyssie M, Squire I, de Belder M, Fox KA, et al. Impact of hospital proportion and volume on primary percutaneous coronary intervention performance in England and Wales. Eur Heart J. 2011;32(6):706-11.	Procedural volumes not defined categorically
Williams SC, Koss RG, Morton DJ, Schmaltz SP, Loeb JM. Case volume and hospital compliance with evidence-based processes of care. International Journal for Quality in Health Care. 2008;20(2):79-87.	Does not report mortality or survival
Xie Y, Rizzo JA, Brown DL. A modified method for estimating volume-outcome relationships: Application to percutaneous coronary intervention. J Med Econ. 2008;11(1):57-70.	Same dataset as an included study
Zhao R, Xu K, Li Y, Qiu M, Han Y. Percutaneous coronary intervention in patients with acute coronary syndrome in Chinese Military Hospitals, 2011-2014: A retrospective observational study of a national registry. BMJ Open. 2018;8(10).	Relationship between hospital or operator volume and PCI

Study	Reason for exclusion
	outcomes is not investigated

Table A.25: Table of studies excluded after full-text review (RQ4)

Study	
Aasa M, Dellborg M, Herlitz J, Svensson L, Grip L. Superior long-term outcome after primary PCI compared to early thrombolysis in acute ST-segment elevation myocardial infarction. Eur Heart J. 2009;30:474.	Not a pharmacoinvasive strategy
Aasa M, Dellborg M, Herlitz J, Svensson L, Grip L. Risk reduction for cardiac events after primary coronary intervention compared with thrombolysis for acute ST-elevation myocardial infarction (five-year results of the Swedish early decision reperfusion strategy trial). American journal of cardiology. 2010;106(12):1685-91.	Duplicate study
Aasa M, Henriksson M, Dellborg M, Grip L, Herlitz J, Levin LA, et al. Cost and health outcome of primary percutaneous coronary intervention versus thrombolysis in acute ST-segment elevation myocardial infarction-Results of the Swedish Early Decision reperfusion Study (SWEDES) trial. Am Heart J. 2010;160(2):322-8.	Not a pharmacoinvasive strategy
Aboal J, Núñez M, Bosch D, Tirón C, Brugada R, Loma-Osorio P. Primary angioplasty versus fibrinolysis in patients at a distance from a hospital with a catheterization laboratory. Emergencias. 2017;29(2):99-104.	Not a pharmacoinvasive strategy
Addad F, Gouider J, Boughzela E, Kamoun S, Boujenah R, Haouala H, et al. Management of patients treated for acute ST-elevation myocardial infarction in Tunisia: Preliminary results of FAST-MI Tunisia Registry from Tunisian Society of Cardiology and Cardiovascular Surgery. Ann Cardiol Angeiol (Paris). 2015;64(6):439-45.	Not a pharmacoinvasive strategy
Addad F, Mahdhaoui A, Gouider J, Boughzela E, Kamoun S, Boujnah MR, et al. Management of patients with acute ST-elevation myocardial infarction: Results of the FAST-MI Tunisia registry. PLoS One. 2019;14(2).	Not a pharmacoinvasive strategy
Alex AG, Lahiri A, Geevar T, George OK. Observational study comparing pharmacoinvasive strategy with primary percutaneous coronary intervention in patients presenting with ST elevation myocardial infarction to a tertiary care centre in India. J Postgrad Med. 2018;64(2):80-5.	Outcomes are not risk-adjusted
Al-Zakwani I, Zubaid M, Al-Riyami A, Alanbaei M, Sulaiman K, Almahmeed W, et al. Primary coronary intervention versus thrombolytic therapy in myocardial infarction patients in the Middle East. Int J Clin Pharm. 2012;34(3):445-51.	Not a pharmacoinvasive strategy
Arablinsky AV, Khairutdinov YR, Tankhielevich BM. Clinical results of the endovascular treatment of patients with ST-elevation myocardial infarction. Interactive Cardiovascular and Thoracic Surgery. 2011;12:S87-S8.	Conference papers and abstracts where the full paper is unobtainable
Armstrong PW, Gershlick A, Goldstein P, Wilcox R, Danays T, Bluhmki E, et al. The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study. Am Heart J. 2010;160(1):30-5.e1.	Not primary research
Ayoub DGE, El-Maghraby KM, Hasan-Ali H, Youssef AAA. Primary percutaneous coronary intervention versus early routine postfibrinolysis percutaneous coronary intervention for ST-elevation myocardial infarction. European heart journal, supplement. 2017;19:F2-.	Conference papers and abstracts where the full paper is unobtainable
Bainey K, Tran D, Potluri R, Carter P, Welsh RC, Kaul P. Regional differences in process of care and clinical outcome among patients with ST-elevation myocardial infarction in Canada and the United Kingdom. Eur Heart J. 2018;39:1257.	No relevant primary outcomes
Bainey K, Zheng Y, Brass N, Tyrrell B, Leung R, Westerhout C, et al. A real world comparison of a pharmacoinvasive versus primary PCI strategy in ST-elevation myocardial infarction: ST-segment	Conference papers and abstracts where the full paper is unobtainable

Study	
recovery and clinical outcome. Eur Heart J. 2018;39:555.	
Bainey KR, Fresco C, Zheng Y, Halvorsen S, Carvalho A, Ostojic M, et al. Implications of ischaemic area at risk and mode of reperfusion in ST-elevation myocardial infarction. Heart. 2016;102(7):527-33.	Conference papers and abstracts where the full paper is unobtainable
Balanescu SM, Benedek I, Nedelciuc I, Deleanu D, Dobreanu D, Olinic D, et al. Reperfusion therapy and inhospital outcome of patients treated by primary PCI vs non-invasive treatment. Data from a 13 years Registry for ST-elevation myocardial infarction in Romania (RO-STEMI). European heart journal, supplement. 2010;12:F53-F4.	Conference papers and abstracts where the full paper is unobtainable
Benziger CP, Mullvain R, Moran P, Solaiman R, Regal R, Hitz P, et al. Long-term outcomes after ST-elevation myocardial infraction after reducing fibrinolytic use in a rural cohort. Circulation. 2019;139.	Conference papers and abstracts where the full paper is unobtainable
Beri A, Printz M, Hassan A, Babb JD. Fibrinolysis versus primary percutaneous intervention in ST-elevation myocardial infarction with long interhospital transfer distances. Clin Cardiol. 2010;33(3):162-7.	Not a pharmacoinvasive strategy
Bernardi G, Di Chiara A, Armellini I. The acute myocardial infarction with ST segment elevation Udine registry (Come-to-Udine): predictors of 3 years mortality. J Cardiovasc Med (Hagerstown). 2009;10(6):474-84.	Not a pharmacoinvasive strategy
Bodí V, Rumiz E, Merlos P, Nunez J, López-Lereu MP, Monmeneu JV, et al. One-week and 6-month cardiovascular magnetic resonance outcome of the pharmacoinvasive strategy and primary angioplasty for the reperfusion of ST-segment elevation myocardial infarction. Rev Esp Cardiol. 2011;64(2):111-20.	Not a pharmacoinvasive strategy
Boivineau C, Orion L, Dimet J, Boiffard E. Indications for fibrinolysis in patients with ST-segment elevation myocardial infarction: From guidelines to practice. Ann Cardiol Angeiol (Paris). 2016;65(5):377.	Conference papers and abstracts where the full paper is unobtainable
Bueno H, Betriu A, Heras M, Alonso JJ, Cequier A, García EJ, et al. Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) randomized trial and pooled analysis with previous studies. Eur Heart J. 2011;32(1):51-60.	Not a pharmacoinvasive strategy
Chan W, Clark DJ, Ajani AE, Andrianopoulos N, Brennan AL, Reid CM, et al. Short- and long-term clinical outcomes in patients undergoing rescue percutaneous coronary intervention compared with primary percutaneous coronary intervention in ST-elevation myocardial infarction. J Am Coll Cardiol. 2010;55(10):A209.E1967.	Conference papers and abstracts where the full paper is unobtainable
Chava S, Raza S, El-Haddad MA, Priest J, Ashikaga T, Dauerman HL. A regional pharmacoinvasive PCI strategy incorporating selected bleeding avoidance strategies. Coron Artery Dis. 2015;26(1):30-6.	Outcomes are not risk-adjusted
Claeys MJ, de Meester A, Convens C, Dubois P, Boland J, De Raedt H, et al. Contemporary mortality differences between primary percutaneous coronary intervention and thrombolysis in ST-segment elevation myocardial infarction. Arch Intern Med. 2011;171(6):544-9.	Not a pharmacoinvasive strategy
Claeys MJ, De Meester A, Convens C, Dubois P, Boland J, Sinnaeve P, et al. Is the mortality benefit of primary PCI over thrombolysis also present in diabetic STEMI patients? A population study of STEMI patients. Eur Heart J. 2009;30:894.	Conference papers and abstracts where the full paper is unobtainable
Colmenero-Ruiz M, Reina-Toral A, Expósito- Ruiz M, García-Pérez C, De Antonio-Martin E, Bermudez-Tamayo C, et al. Outcomes of patients with STEMI according to type of reperfusion used in Andalusia (southern Spain). European Journal of Epidemiology. 2012;27(1):S83.	Conference papers and abstracts where the full paper is unobtainable
Cook J, Carter A, Travers A, Brown R, Cain E, Swain J, et al. Outcomes of a provincial cardiac reperfusion strategy: A	Conference papers and abstracts where the full

Study	
population-based, retrospective cohort study. Canadian Journal of Emergency Medicine. 2016;18:S38-S9.	paper is unobtainable
Czarnecki A, Welsh RC, Yan RT, DeYoung JP, Gallo R, Rose B, et al. Reperfusion Strategies and Outcomes of ST-Segment Elevation Myocardial Infarction Patients in Canada: Observations From the Global Registry of Acute Coronary Events (GRACE) and the Canadian Registry of Acute Coronary Events (CANRACE). Canadian journal of cardiology. 2012;28(1):40-7.	Not a pharmacoinvasive strategy
Danchin N, Coste P, Ferrières J, Steg PG, Cottin Y, Blanchard D, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: Data from the French registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation. 2008;118(3):268-76.	Not a pharmacoinvasive strategy
Danchin N, Puymirat E, Steg PG, Goldstein P, Schiele F, Belle L, et al. Five-Year survival in patients with ST-Segment-elevation myocardial infarction according to modalities of reperfusion therapy: The French registry on acute ST-elevation and non-ST-Elevation myocardial infarction (FAST-MI) 2005 cohort. Circulation. 2014;129(16):1629-36.	Not a pharmacoinvasive strategy
Dangas G, Stone GW, Weinberg MD, Webb J, Cox DA, Brodie BR, et al. Contemporary outcomes of rescue percutaneous coronary intervention for acute myocardial infarction: comparison with primary angioplasty and the role of distal protection devices (EMERALD trial). Am Heart J. 2008;155(6):1090-6.	Not a pharmacoinvasive strategy
De Luca L, Bolognese L, Casella G, Savonitto S, Gonzini L, Di Chiara A, et al. Modalities of treatment and 30-day outcomes of unselected patients older than 75 years with acute ST-elevation myocardial infarction: data from the BLITZ study. J Cardiovasc Med (Hagerstown). 2008;9(10):1045-51.	Not a pharmacoinvasive strategy
Del Pinto M, Angeli F, Contine A, Repaci S, Verdecchia P, Notaristefano S, et al. ST-Segment resolution after fibrinolysis or primary coronary angioplasty in the first three hours in acute myocardial infarction. Eur Heart J. 2009;30:928.	Conference papers and abstracts where the full paper is unobtainable
Denktas AE, Athar H, Henry TD, Larson DM, Simons M, Chan RS, et al. Reduced-dose fibrinolytic acceleration of ST-segment elevation myocardial infarction treatment coupled with urgent percutaneous coronary intervention compared to primary percutaneous coronary intervention alone results of the AMICO (Alliance for Myocardial Infarction Care Optimization) Registry. JACC Cardiovasc Interv. 2008;1(5):504-10.	Not a pharmacoinvasive strategy
Dery JP, De Larochellière R, Cantin B, Nguyen M, Harvey R, Kouz S, et al. Type of reperfusion therapy and impact on longterm survival in patients with ST-elevation myocardial infarction: Insight from the AMI-québec study. Canadian journal of cardiology. 2011;27(5):S144.	Conference papers and abstracts where the full paper is unobtainable
Dharma S, Andriantoro H, Purnawan I, Dakota I, Basalamah F, Hartono B, et al. Characteristics, treatment and in-hospital outcomes of patients with STEMI in a metropolitan area of a developing country: an initial report of the extended Jakarta Acute Coronary Syndrome registry. BMJ Open. 2016;6(8):e012193.	Not a pharmacoinvasive strategy
Dharma S, Juzar DA, Firdaus I, Soerianata S, Wardeh AJ, Jukema JW. Acute myocardial infarction system of care in the third world. Neth Heart J. 2012;20(6):254-9.	Not a pharmacoinvasive strategy
Espinoza D, Rebaza CP, Araoz O, Espinoza J, Pereda CM, Mantilla A. Clinical presentation, management and outcome of st-elevation myocardial infarction in Peru. European heart journal: acute cardiovascular care. 2015;4:121-2.	Conference papers and abstracts where the full paper is unobtainable
Euctr IT. Comparison of the efficacy and safety of a strategy of pre-hospital fibrinolytic treatment with tenecteplase and additional antiplatelet and antithrombin therapy followed by catheterisation	Not primary research

Study	
within 6-24 hours or rescue coronary intervention versus a strategy of standard primary PCI in patients with acute myocardial infarction within 3 hours of onset of symptoms - STREAM. Http://wwwwhoint/trialsearch/trial2aspx? Trialid=euctr2007-001219-44-it. 2008.	
Falsoleiman H, Fatehi GH, Dehghani M, Shakeri MT, Bayani B, Ahmadi M, et al. Clinical outcome, and survival between primary percutaneous coronary intervention versus fibrinolysis in patients older than 60 years with acute myocardial infarction. Heart Views. 2012;13(4):129-31.	Not a pharmacoinvasive strategy
Faslur Rahuman MB, Jayawardena JB, Francis GR, Mahboob N, Kumara AHTW, Wijesinghe A, et al. A comparison of rescue and primary percutaneous coronary interventions for acute ST elevation myocardial infarction. Indian Heart J. 2017;69 Suppl 1:S57-s62.	Not a pharmacoinvasive strategy
Gagliardi JA, Charask A, Perna E, D'Imperio H, Bono J, Castillo Y, et al. National survey of st-elevation myocardial infarction in argentina (Argen-iam-st). Revista de la Federacion Argentina de Cardiologia. 2017;46(1):15-21.	Non-comparative study
Ganassin FP, Cantarelli MJC, Castello Jr HJ, Gonçalves R, Ribeiro EKP, Guimarães JBF, et al. In-hospital outcomes on patients submitted to primary versus rescue percutaneous coronary intervention. Revista Brasileira de Cardiologia Invasiva. 2013;21(2).	Not a pharmacoinvasive strategy
Gao RL, Han YL, Yang XC, Mao JM, Fang WY, Wang L, et al. Thorombolytic therapy with rescue percutaneous coronary intervention versus primary percutaneous coronary intervention in patients with acute myocardial infarction: A multicenter randomized clinical trial. Chin Med J (Engl). 2010;123(11):1365-72.	Not a pharmacoinvasive strategy
Ge H, Pu J, Li Z, Manka R, Ding H, Xu J, et al. Comparison of instant thrombolysis plus early PCI and primary PCI in stemi patients, view of CMR early after reperfusion therapy. American journal of cardiology. 2013;111(7):8B.	Conference papers and abstracts where the full paper is unobtainable
Ge H, Pu J, Li Z, Xu J, He B. Comparison of pharmacoinvasion and primary PCI strategy in stemi patients, evidence from cardiac magnetic resonance imaging. J Am Coll Cardiol. 2013;62(18):B74-B5.	Conference papers and abstracts where the full paper is unobtainable
Grajek S, Lesiak M, Araszkiewicz A, Pyda M, Skorupski W, Grygier M, et al. Short- and long-term mortality in patients with ST-elevation myocardial infarction treated with different therapeutic strategies. Results from WIelkopolska REgional 2002 Registry (WIRE Registry). Kardiol Pol. 2008;66(2):154-63; discussion 64.	Not a pharmacoinvasive strategy
Greig D, Corbalán R, Castro P, Campos P, Lamich R, Yovaniniz P. Mortality of patients with ST-elevation acute myocardial infarction treated with primary angioplasty or thrombolysis. Revista Medica de Chile. 2008;136(9):1098-106.	Not a pharmacoinvasive strategy
Han YL, Liu JN, Jing QM, Ma YY, Jiang TM, Pu K, et al. The efficacy and safety of pharmacoinvasive therapy with prourokinase for acute ST-segment elevation myocardial infarction patients with expected long percutaneous coronary intervention-related delay. Cardiovasc Ther. 2013;31(5):285-90.	Not a pharmacoinvasive strategy
He X. Early routine post-fibrinolysis angioplasty benefits more patients with acute ST-elevation myocardial infarction. Cardiology (switzerland). 2013;126:164.	Not a pharmacoinvasive strategy
He XZ. Early routine post-fibrinolysis angioplasty compared to primary angioplasty in patients with acute st elevation myocardial infarction. Heart. 2013;99:A68-.	Duplicate study
Helal AM, Shaheen SM, Elhammady WA, Ahmed MI, Abdel-Hakim AS, Allam LE. Primary PCI versus pharmacoinvasive strategy for ST elevation myocardial infarction. Int J Cardiol Heart Vasc. 2018;21:87-93.	Not a pharmacoinvasive strategy
Hira RS, Bhatt D, Fonarow G, Heidenreich P, Ju C, Virani S, et al. Temporal trends in care and outcomes of patients receiving	Not a pharmacoinvasive strategy

Study	
fibrinolytic therapy compared to primary percutaneous coronary intervention in the get with the guidelines coronary artery disease (GWTG-CAD) registry. J Am Coll Cardiol. 2015;65(10):A68.	
Jäger B, Farhan S, Kalla K, Glogar HD, Christ G, Karnik R, et al. One-year mortality in patients with acute ST-elevation myocardial infarction in the Vienna STEMI registry. Wien Klin Wochenschr. 2015;127(13-14):535-42.	Not a pharmacoinvasive strategy
Jezewski T, Konopa B, Tarchalski J, Kasprzak JD. Comparison of clinical results and life quality after myocardial infarction therapy with primary percutaneous coronary intervention and fibrinolytic angents. Pol Arch Med Wewn. 2009;119(1-2):26-31.	Not a pharmacoinvasive strategy
Jomaa W, Ben Abdeljelil O, Ben Tekaya MA, Chamtouri I, Ben Hamda K, Maatouk F. TCTAP A-028 Prognostic Significance of Reperfusion Delays in Patients Presenting for ST-elevation Myocardial Infarction in the Tunisian Context. J Am Coll Cardiol. 2019;73(15):S14.	Conference papers and abstracts where the full paper is unobtainable
Kapeliovich M, Naara S, Roguin A, Dragu R, Bahout F, Agmon Y, et al. Thrombolytic therapy versus primary PCI in early-comers STEMI patients. European heart journal: acute cardiovascular care. 2013;2:19.	Conference papers and abstracts where the full paper is unobtainable
Karam N, Lambert Y, Tafflet M, Bataille S, Benamer H, Caussin C, et al. Changes in reperfusion strategy over time for ST segment elevation myocardial infarction in the Greater Paris Area: results from the e-MUST Registry. Int J Cardiol. 2013;168(6):5149-55.	Not a pharmacoinvasive strategy
Karam N, Tafflet M, Bataille S, Juliard JM, Letarnec JY, Capitani GA, et al. Reperfusion strategies in greater paris area and associated mortality in a 6-year registry. Eur Heart J. 2011;32:873.	Duplicate study
Kevin RB, Ferguson C, Ibrahim Q, Tyrrell B, Armstrong P, Welsh R. Impact of reperfusion strategy on aborted myocardial infarction: Insights from a large Canadian STEMI clinical registry. J Am Coll Cardiol. 2013;61(10):E94.	Wrong comparator
Khalili H, Talasaz AH, Jenab Y, Salarifar M. Clinical characteristics and risk assessment of ST-segment elevation myocardial infarction patients of an Iranian referral center. J Cardiovasc Med (Hagerstown). 2012;13(11):708-15.	Not a pharmacoinvasive strategy
Khan A, Boyle A, Fletcher P, Savage L, Stewart P, Williams T. Pre-hospital thrombolysis for ST-segment elevation myocardial infarction (STEMI). Heart Lung and Circulation. 2015;24:S161.	Not a pharmacoinvasive strategy
Khan A, Williams T, Savage L, Stewart P, Bhagwandeen R, Fletcher P, et al. Pre-hospital thrombolysis and transfer achieves optimal outcomes in ST-segment elevation myocardial infarction despite large transport distances-realworld two year follow up. Heart Lung and Circulation. 2016;25:S58-S9.	Duplicate study
Khan AA, Williams T, Al-Omary MS, Feeney AL, Majeed T, Savage L, et al. Pre-hospital Thrombolysis for ST-segment Elevation Myocardial Infarction in Regional Australia: Long Term Follow Up. Intern Med J. 2019.	Duplicate study
Khan AA, Williams T, Savage L, Stewart P, Ashraf A, Davies AJ, et al. Pre-hospital thrombolysis in ST-segment elevation myocardial infarction: a regional Australian experience. Medical Journal of Australia. 2016;205(3):121-5.	Duplicate study
Khan AA, Williams T, Savage L, Stewart P, Fletcher P, Boyle A. Pre-hospital thrombolysis versus primary percutaneous coronary intervention for st-segment elevation myocardial infarction in regional Australia: Real world long term follow up. J Am Coll Cardiol. 2016;67(13):613.	Not a pharmacoinvasive strategy
Khripun A, Malevannyi M, Kulikovskikh Y. Three-year outcomes of pharmaco-invasive reperfusion for STEMI treatment. EuroIntervention. 2015.	Conference papers and abstracts where the full paper is unobtainable
Khripun AV, Malevannyi MV, Kulikovskikh Y. Pharmaco-invasive strategy for ST-segment elevation myocardial infarction treatment.	Conference papers and abstracts where the full

Study	
Eur Heart J. 2013;34:1029.	paper is unobtainable
Khripun AV, Malevannyi MV, Kulikovskikh Y. Long-term results of pharmaco-invasive strategy for ST-segment elevation myocardial infarction treatment. Eur Heart J. 2014;35:1173.	Conference papers and abstracts where the full paper is unobtainable
Kocayigit I, Yaylaci S, Osken A, Aydin E, Sahinkus S, Can Y, et al. Comparison of effects of thrombolytic therapy and primary percutaneous coronary intervention in elderly patients with acute ST-segment elevation myocardial infarction on in-hospital, six-month, and one-year mortality. Arch Med Sci Atheroscler Dis. 2019;4:e82-e8.	Not a pharmacoinvasive strategy
Koeth O, Nibbe L, Arntz HR, Dirks B, Ellinger K, Genzwürker H, et al. Fate of patients with prehospital resuscitation for ST-elevation myocardial infarction and a high rate of early reperfusion therapy (Results from the PREMIR [Prehospital Myocardial Infarction Registry]). American journal of cardiology. 2012;109(12):1733-7.	Not a pharmacoinvasive strategy
Koeth O, Zahn R, Bauer T, Juenger C, Gitt AK, Senges J, et al. Primary percutaneous coronary intervention and thrombolysis improve survival in patients with ST-elevation myocardial infarction and pre-hospital resuscitation. Resuscitation. 2010;81(11):1505-8.	Not a pharmacoinvasive strategy
Koeth O, Zahn R, Bauer T, Juenger C, Schwarz AK, Senges J, et al. Primary PCI and thromboysis in survivors of prehospital resuscitation. Eur Heart J. 2009;30:693.	Duplicate study
Koeth O, Zahn R, Gitt AK, Bauer T, Juenger C, Senges J, et al. Clinical benefit of early reperfusion therapy in patients with ST-elevation myocardial infarction usually excluded from randomized clinical trials (results from the Maximal Individual Therapy in Acute Myocardial Infarction Plus [MITRA Plus] registry). Am J Cardiol. 2009;104(8):1074-7.	Not a pharmacoinvasive strategy
Koeth O, Zahn R, Heer T, Bauer T, Juenger C, Klein B, et al. Gender differences in patients with acute ST-elevation myocardial infarction complicated by cardiogenic shock. Clin Res Cardiol. 2009;98(12):781-6.	Not a pharmacoinvasive strategy
Kumar VVNPM, Vohara J, Biyandu P, V S, Goddu MS, Chaganti VR. Primary percutaneous intervention vs thrombolytic therapy in acute anterior wall STEMI with qRBBB - Single center study. Indian Heart J. 2018;70:S62-S3.	Conference papers and abstracts where the full paper is unobtainable
Lambert LJ, Xiao Y, Kouz S, Rinfret S, Segal E, Ross D, et al. Comparison of outcomes by type of treatment for patients with ST-elevation myocardial infarction (STEMI) who presented to hospitals without percutaneous coronary intervention (PCI) facilities in Quebec, Canada. Circulation: Cardiovascular Quality and Outcomes. 2013;6(3).	Conference papers and abstracts where the full paper is unobtainable
Lambert LJ, Xiao Y, Rinfret S, L'Allier P, Segal E, Maire S, et al. A comparison of outcomes of patients with ST-elevation myocardial infarction by type of hospital and choice of treatment: Results of a Québec-wide, systematic field evaluation (2008-2009). Canadian journal of cardiology. 2012;28(5):S378-S9.	Conference papers and abstracts where the full paper is unobtainable
Larson DM, Duval S, Sharkey SW, Garberich RF, Madison JD, Stokman PJ, et al. Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. Eur Heart J. 2012;33(10):1232-40.	Not a pharmacoinvasive strategy
Laurin C, Auffret V, Leurent G, Didier R, Filippi E, Hacot JP, et al. Thrombolysis Versus Primary Percutaneous Coronary Intervention For ST-segment Elevation Myocardial Infarction In Elderly Patients. Archives of Cardiovascular Diseases Supplements. 2019;11(1):e284.	Conference papers and abstracts where the full paper is unobtainable
Lee A, Pu A, Ramanathan KR, Perry M, Gao M, Wong GC. Impact of the type and timeliness of reperfusion on left ventricular dysfunction amongst survivors of st elevation myocardial infarction (STEMI) within a regional model of stemi care: Insights from the	Conference papers and abstracts where the full paper is unobtainable

Study	
vancouver coastal health authority stemi initiative. Canadian journal of cardiology. 2011;27(5):S221-S2.	
Lee S, Chow J, Tan CH, Tan KS, Lingamanaicker J, Lim V, et al. Revascularisation strategy for young patients presenting with ST elevation myocardial infarction: Comparing outcomes between PCI versus thrombolysis. American journal of cardiology. 2011;107(8):42A-3A.	Conference papers and abstracts where the full paper is unobtainable
Lee SY, Bae JW, Kim SM, Hwang KK, Kim DW, Cho MC. Which reperfusion therapy is better by primary percutaneous coronary intervention versus thrombolysis in patients with stsegment elevation myocardial infarction within 3 hours of the onset of symptoms in des Era? : From Korea Acute Myocardial Infarction Registry (KAMIR). American journal of cardiology. 2012;109(7):7S-8S.	Conference papers and abstracts where the full paper is unobtainable
Lee SY, Kim M, Lee JH, Kim SM, Bae JW, Hwang KK, et al. Which reperfusion therapy is better in patients with ST-segment elevation myocardial infarction within 3 hours of the onset of symptoms? From Korea Acute Myocardial Infarction Registry (KAMIR). J Am Coll Cardiol. 2014;63(12):A216.	Conference papers and abstracts where the full paper is unobtainable
Levi Y, Frimerman A, Shotan A, Shochat M, Blondheim DS, Segev A, et al. Primary Percutaneous Coronary Intervention Versus In-hospital thrombolysis as Reperfusion Therapy in Early-Arriving Low-risk STEMI Patients. Isr Med Assoc J. 2017;19(6):345-50.	Not a pharmacoinvasive strategy
Livia NM, Antonio CC, Goncalves Jr I, Barbosa A, Tarkieltaub E, Antonio CM, et al. Pharmaco invasive therapy in STEMI patients in emerging countries, different from the developed world, could decrease mortality compared to usual treatment. J Am Coll Cardiol. 2013;61(10):E61.	Conference papers and abstracts where the full paper is unobtainable
Magnavacchi P, Paganelli C, Tondi S, Cappelli C. Long-term clinical outcome of primary pci versus fibrinolysis for st-elevation myocardial infarction: Results from a single center prospective registry. Giornale italiano di cardiologia. 2012;13(5):164S-5S.	Conference papers and abstracts where the full paper is unobtainable
Mahendiran T, McKenzie D, Newton J, Rowe R, Clarkson J, Dayer M. Re-introduction of pre-hospital thrombolysis could improve stemi outcomes when primary percutaneous coronary intervention is delayed. Heart. 2016;102:A70-A1.	Conference papers and abstracts where the full paper is unobtainable
Mahmaljy H, Aguirre FV, Al-Akchar M, Kalathiya R, Nandish S, Besser SA, et al. Long-term (10-year) mortality of ST elevation myocardial infarction patients directly admitted to facilities for primary percutaneous coronary intervention vs inter-hospital transfer: Impact of "targeted" use of pre-transfer fibrinolytic therapy. Circulation. 2017;136.	Conference papers and abstracts where the full paper is unobtainable
Maleki ND, Van de Werf F, Goldstein P, Adgey JA, Lambert Y, Sulimov V, et al. Aborted myocardial infarction in ST-elevation myocardial infarction: insights from the STrategic Reperfusion Early After Myocardial infarction trial. Heart. 2014;100(19):1543-9.	No relevant primary outcomes
Malik F. Pharmaco-invasive therapy: Hybrid approach as a feasible alternative for STEMI in developing countries. EuroIntervention. 2016:76.	Conference papers and abstracts where the full paper is unobtainable
Manari A, Tomasi C, Guiducci V, Zanoni P, Pignatelli G, Giacometti P. Time to treatment and ST-segment resolution in high-risk patients with acute myocardial infarction transferred from community hospitals for coronary angioplasty after pharmacological treatment. J Cardiovasc Med (Hagerstown). 2008;9(1):32-8.	Not a pharmacoinvasive strategy
Markov VA, Vyshlov EV, Sevast'ianova DS, Filiushkina V, Dem'ianov SV, Maksimov IV, et al. Comparative efficacy of pharmacoinvasive strategy of myocardial reperfusion and primary angioplasty in patients with acute ST elevation myocardial infarction. Kardiologiia. 2013;53(10):10-5.	Preliminary study
Medina HM, Cannon CP, Fonarow GC, Grau-Sepulveda MV,	Not a pharmacoinvasive

Study	
Hernandez AF, Frank Peacock W, et al. Reperfusion strategies and quality of care in 5339 patients age 80 years or older presenting with ST-elevation myocardial infarction: analysis from get with the guidelines-coronary artery disease. Clin Cardiol. 2012;35(10):632-40.	strategy
Mehta RH, Gitt AK, Jünger C, Zeymer U, Schiele R, Zahn R, et al. Body mass index and effectiveness of reperfusion strategies: Implications for the management of patients with ST-elevation myocardial infarction. J Interv Cardiol. 2008;21(1):8-14.	Not a pharmacoinvasive strategy
Michael A, Coley K, Menon M, Devlin G, Nunn C. Rescue percutaneous intervention in St elevation myocardial infarction-impact of regional transfer delays in the midland region: Time does matter. J Am Coll Cardiol. 2018;71(11).	Conference papers and abstracts where the full paper is unobtainable
Mochmann HC, Schlippenbach J, Arntz HR. Lower long term mortality with PCI after out-of hospital fibrinolysis within 3 h of symptom onset as compared to primary PCI in patients with STEMI. Resuscitation. 2010;81(2):S26.	Conference papers and abstracts where the full paper is unobtainable
Morales M, Oliva P, Rivas F, Ponce P, Domínguez P, Gallardo V, et al. Fibrinolytic therapy vs angioplasty. Are there more complications depending on the choice of reperfusion technique? Intensive Care Medicine Experimental. 2018;6.	Conference papers and abstracts where the full paper is unobtainable
Nct. Pharmacoinvasive Strategy vs. Primary PCI in STEMI: A Prospective Registry in a Large Geographical Area (PHASE-MX). 2019.	Not primary research
Norgaz T, Gorgulu S, Aksu H, Hobikoglu G, Ergelen M, Onturk E, et al. Comparison of primary percutaneous coronary intervention and streptokinase for acute isolated inferior ST elevation myocardial infarction with a predicted low risk profile. Med Sci Monit. 2010;16(9):Cr416-22.	Not a pharmacoinvasive strategy
Ogunbayo GO, Misumida N, Ayoub K, Hailemariam Y, Hillerson D, Elbadawi A, et al. Temporal trends, characteristics and outcomes of fibrinolytic therapy for ST-elevation myocardial infarction among patients 80 years or older. Catheter Cardiovasc Interv. 2018;92(7):E425-e32.	Not a pharmacoinvasive strategy
Paul A, George PV. Left ventricular global longitudinal strain following revascularization in acute ST elevation myocardial infarction – A comparison of primary angioplasty and Streptokinase-based pharmacoinvasive strategy. Indian Heart J. 2017;69(6):695-9.	Outcomes are not risk-adjusted
Peiyuan H, Jingang Y, Haiyan X, Xiaojin G, Ying X, Yuan W, et al. The comparison of the outcomes between primary PCI, fibrinolysis, and no reperfusion in patients ≥ 75 years old with ST-segment elevation myocardial infarction: Results from the Chinese acute myocardial infarction (CAMI) registry. PLoS One. 2016;11(11).	Not a pharmacoinvasive strategy
Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation. 2011;124(23):2512-21.	Not a pharmacoinvasive strategy
Politi A, Martinoni A, Klugmann S, Zanini R, Onofri M, Guagliumi G, et al. LombardIMA: a regional registry for coronary angioplasty in ST-elevation myocardial infarction. J Cardiovasc Med (Hagerstown). 2011;12(1):43-50.	Not a pharmacoinvasive strategy
Posnenkova OM, Kiselev AR, Popova YV, Gridnev VI, Prokhorov MD, Dovgalevsky PY. Impact of patient-related and treatment-related factors on in-hospital mortality of patients with ST-elevation myocardial infarction: Data of Russian Acute Coronary Syndrome Registry. Cor et Vasa. 2014;56(3):e217-e27.	Not a pharmacoinvasive strategy
Puymirat E, Caudron J, Steg PG, Lemesle G, Cottin Y, Coste P, et al. Prognostic impact of non-compliance with guidelines-recommended times to reperfusion therapy in ST-elevation	Not a pharmacoinvasive strategy

Study	
myocardial infarction. The FAST-MI 2010 registry. European heart journal: acute cardiovascular care. 2017;6(1):26-33.	
Puymirat E, Lorgis L, Coste P, Charpentier S, Lemesle G, Durand E, et al. Impact on early complications of non-compliance with guidelines-recommended timelines for reperfusion therapy in STEMI patients. The FAST-MI 2010 registry. Eur Heart J. 2012;33:203-4.	Conference papers and abstracts where the full paper is unobtainable
Rankin K, Brennan A, Andrianopoulos N, Sebastian M, Freeman M, Yip T, et al. Comparative outcome of patients undergoing percutaneous coronary intervention (PCI) following fibrinolysis or primary PCI for ST-elevation myocardial infarction. Heart Lung and Circulation. 2015;24:S268.	Conference papers and abstracts where the full paper is unobtainable
Rodriguez De Leiras Otero S, Prado Gotor B, Sayago Silva I, Vizcaino Arellano M, Marcos Sanchez F, Carrascosa Rosillo C, et al. Primary percutaneous coronary intervention and culprit vessel revascularisation versus thrombolysis and early complete revascularisation: Comparison of two strategies. EuroIntervention. 2010;6.	Conference papers and abstracts where the full paper is unobtainable
Sanatkar M, Shemirani H, Sanei H, Pourmoghaddas M, Rabiei K. Effects of streptokinase on reflow in rescue percutaneous coronary intervention. ARYA Atheroscler. 2013;9(1):22-8.	Not a pharmacoinvasive strategy
Schwartz R, Weiss AT, Leibowitz D, Rot D, Pollak A, Lotan C, et al. Thrombolysis followed by coronary angiography versus primary percutaneous coronary intervention in non-anterior ST-elevation myocardial infarction. J Invasive Cardiol. 2013;25(12):632-6.	Not a pharmacoinvasive strategy
Seguy B, Naibo D, Casassus F, Gerbaud E, Leroux L, Jais C, et al. A single pre-hospital enoxaparine protocole for all STEMI admitted to ICU: One year experience and one year follow-up in Haut Lévêque cardiological hospital. Archives of Cardiovascular Diseases Supplements. 2012;4(1):21.	Conference papers and abstracts where the full paper is unobtainable
Selvarajah S, Fong AYY, Selvaraj G, Haniff J, Hairi NN, Bulgiba A, et al. Impact of cardiac care variation on St-elevation myocardial infarction outcomes in Malaysia. American journal of cardiology. 2013;111(9):1270-6.	Not a pharmacoinvasive strategy
Sen N, Jain A, Tanwar S, Kishore R. Precath thrombolysis with single dose of reteplase followed by percutaneous coronary intervention (PCI) versus double dose of reteplase with PCI or percutaneous coronary intervention alone for acute st elevation myocardial infarction. Catheterization and cardiovascular interventions. 2018;91:S43-S4.	Conference papers and abstracts where the full paper is unobtainable
Shaheen SM, Elhammady WAA, Ahmed MI, Abdel-Hakim AS, Allam LE, Helal AM. Primary PCI versus early routine Post Fibrinolysis PCI for ST elevation myocardial infarction. Eur Heart J Cardiovasc Imaging. 2016;17:i47.	Duplicate study
Shavadia J, Bainey K, Tyrrell B, Brass N, Paterson C, Knapp D, et al. Half-dose tenecteplase compared to conventional stsegment myocardial infarction (stemi) reperfusion strategies in the elderly: An observational analysis. Canadian journal of cardiology. 2015;31(10):S20-S1.	Conference papers and abstracts where the full paper is unobtainable
Shavadia J, Welsh R, Gershlick A, Zheng Y, Huber K, Halvorsen S, et al. Relationship Between Arterial Access and Outcomes in ST-Elevation Myocardial Infarction With a Pharmacoinvasive Versus Primary Percutaneous Coronary Intervention Strategy: Insights From the STrategic Reperfusion Early After Myocardial Infarction (STREAM) Study. J Am Heart Assoc. 2016;5(6).	Wrong comparator
Shavadia J, Zheng Y, Dianati Maleki N, Huber K, Halvorsen S, Goldstein P, et al. Infarct Size, Shock, and Heart Failure: Does Reperfusion Strategy Matter in Early Presenting Patients With ST-Segment Elevation Myocardial Infarction? J Am Heart Assoc. 2015;4(8):e002049.	No relevant primary outcomes
Shetty S, Shetty P. Bleeding and in-hospital outcomes in STEMI	Conference papers and

Study	
patients treated with combination of potent thienopyridine and fibrinolytic therapy, primary percutaneous intervention, rescue percutaneous intervention or routine percutaneous intervention post fibrinolytic therapy in a regional setting. Heart Lung and Circulation. 2017;26:S201.	abstracts where the full paper is unobtainable
Shilova AS. Long term outcomes in patients with st-segment elevation acure coronary syndrome in the application of a pharmacoinvasive approach and primary percutaneous coronary intervention: results of a two-year follow-up in real clinical practice conditions. 2016.	Outcomes are not risk-adjusted
Shrivastav R, Pati P, Perimbeti S, Tamis-Holland J. Prevalence of mechanical complications and associated mortality in patients with St-segment elevation myocardial infarction (STEMI) treated with thrombolysis (TT) compared to primary-PCI (P-PCI): A nationwide study using national inpatient sample (NIS). Circulation. 2018;138.	Conference papers and abstracts where the full paper is unobtainable
Sim DS, Jeong MH, Ahn Y, Kim YJ, Chae SC, Hong TJ, et al. Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention in Patients With ST-Segment-Elevation Myocardial Infarction: A Propensity Score-Matched Analysis. Circ Cardiovasc Interv. 2016;9(9).	Not a pharmacoinvasive strategy
Sinnaeve P, Armstrong P, Gershlick A, Goldstein P, Wilcox R, Danays T, et al. One year mortality in STEMI patients randomized to primary PCI or a pharmaco-invasive strategy. The stream 1 year follow-up. Circulation. 2013;128(24):2709.	Not primary research
Sinnaeve PR, Danays T, Bogaerts K, Van de Werf F, Armstrong PW. Drug Treatment of STEMI in the Elderly: Focus on Fibrinolytic Therapy and Insights from the STREAM Trial. Drugs Aging. 2016;33(2):109-18.	Conference papers and abstracts where the full paper is unobtainable
Smith LG, Duval S, Tannenbaum MA, Johnson Brown S, Poulose AK, Iannone LA, et al. Are the results of a regional ST-elevation myocardial infarction system reproducible? Am J Cardiol. 2012;109(11):1582-8.	Wrong comparator
Solhpour A, Chang KW, Arain SA, Balan P, Zhao Y, Loghin C, et al. Comparison of 30-day mortality and myocardial scar indices for patients treated with prehospital reduced dose fibrinolytic followed by percutaneous coronary intervention versus percutaneous coronary intervention alone for treatment of ST-elevation myocardial infarction. Catheter Cardiovasc Interv. 2016;88(5):709-15.	Not a pharmacoinvasive strategy
Solhpour A, Chang KW, Balan P, Cai C, Sdringola S, Denktas AE, et al. Comparison of outcomes for patients ≥75 years of age treated with pre-hospital reduced-dose fibrinolysis followed by percutaneous coronary intervention versus percutaneous coronary intervention alone for treatment of st-elevation myocardial infarction. American journal of cardiology. 2014;113(1):60-3.	Not a pharmacoinvasive strategy
Studenčan M, Kovář F, Hricák V, Kurray P, Goncalvesová E, Šimková I, et al. Two-year survival of STEMI patients in Slovakia. An analysis of the SLOVak registry of Acute Coronary Syndromes (SLOVAKS). Cor et Vasa. 2014;56(4):e297-e303.	Not a pharmacoinvasive strategy
Sulimov VA. Thrombolysis or primary PCI for myocardial infarction with ST-segment elevation? The STREAM trial (Strategic Reperfusion Early after Myocardial Infarction). Rational pharmacotherapy in cardiology. 2013;9(6):640-9.	Duplicate study
Sultan EZM, Rabea HM, abdelmeguid KR, Mahmoud HB. Transradial artery approach in STEMI patients reperfused early and late by either primary PCI or pharmaco-invasive approach. Egyptian heart journal. 2018;70(1):1-7.	Wrong study design
Tatu-Chitoiu G, Arafat R, Deleanu D, Vinereanu D, Udroiu C, Petris A. Impact of the Romanian national programme for interventional therapy in ST-elevation myocardial infarction. EuroIntervention. 2012;8 Suppl P:P126-32.	Conference papers and abstracts where the full paper is unobtainable

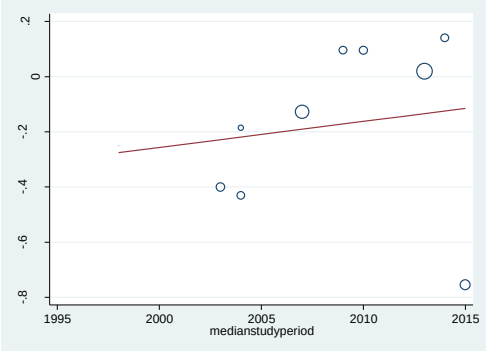
Study	
Tatu-Chitoiu GP, Arafat R, Deleanu D, Capalneanu R, Macarie C, Dorobantu M, et al. Impact on the in-hospital mortality of the Romanian national programme for interventional therapy in ST-elevation myocardial infarction. European heart journal: acute cardiovascular care. 2012;1:102.	Duplicate study
Tatu-Chitoiu GP, Arafat R, Deleanu D, Udroiu C, Petris AO, Vinereanu D. Major impact on the in-hospital mortality of the Romanian national program for interventional therapy in ST-elevation myocardial infarction. RO-STEMI registry. Eur Heart J. 2013;34:234.	Conference papers and abstracts where the full paper is unobtainable
Tatu-Chitoiu GP, Deleanu D, Arafat R, Zarma L, Calmac L, Macarie C, et al. Primary coronary angioplasty in patients with STtelevation myocardial infarction in the Bucharest (Romania) area. Over the stent for life initiative target one year after the network opening. European heart journal: acute cardiovascular care. 2012;1:59.	Conference papers and abstracts where the full paper is unobtainable
Tatu-Chitoiu GP, Deleanu D, Petris A, Macarie C, Arsenescu Georgescu C, Petrescu L, et al. A national PCI network and a pharmacoinvasive strategy, keys of success of the Romanian STEMI program. Eur Heart J. 2014;35:545-6.	Conference papers and abstracts where the full paper is unobtainable
Tatu-Chitoiu GP, Deleanu D, Petris A, Macarie C, Petrescu L, Arsenescu Georgescu C, et al. Lower in-hospital mortality in STEMI patients with postponed angioplasty after successful pre-transfer medication compared with primary angioplasty. RO-STEMI registry data. Eur Heart J. 2014;35:310.	Not a pharmacoinvasive strategy
Tramullas A, Loma-Osorio A, Vaquero J, Castaneda A, Torres A, Artaetxeberria J, et al. Results of coronary angiography (culprit artery situation) in STEMI patients undergoing pharmacoinvasive strategy. The BIHOTZEZ registry. European heart journal: acute cardiovascular care. 2015;4:314.	Conference papers and abstracts where the full paper is unobtainable
Tran DT, Welsh RC, Ohinmaa A, Thanh NX, Kaul P. Temporal Trends of Reperfusion Strategies and Hospital Mortality for Patients With STEMI in Percutaneous Coronary Intervention–Capable Hospitals. Canadian journal of cardiology. 2017;33(4):485-92.	Not a pharmacoinvasive strategy
Tungsubutra W. Rescue percutaneous coronary intervention for failed thrombolytic therapy in Thailand's largest university-based tertiary care hospital. Catheterization and cardiovascular interventions. 2016;87:S20.	Conference papers and abstracts where the full paper is unobtainable
Tungsubutra W, Chichareon P, Tresukosol D, Chotinaiwattrakul C, Phankingthongkum R, Wongpraparut N, et al. In-Hospital Outcomes after Rescue Percutaneous Coronary Intervention in Patients with ST Segment Elevation Myocardial Infarction. J Med Assoc Thai. 2016;99(6):645-52.	Not a pharmacoinvasive strategy
Vasiljevic-Pokrajcic Z, Krljanac G, Panic G, Davidovic G, Ilic S, Asanin M, et al. Clinical characteristics and outcome of STEMI patients with early (3 hours) presentation treated by primary PCI or fibrinolysis therapy. Eur Heart J. 2014;35:986-7.	Conference papers and abstracts where the full paper is unobtainable
Vasiljevic-Pokrajcic Z, Krljanac G, Panic G, Majstorovic M, Zdravkovic M, Saric J, et al. Mortality rate and prognostic factors in STEMI patients in Serbia, country in transition. European heart journal: acute cardiovascular care. 2014;3(2):106-7.	Conference papers and abstracts where the full paper is unobtainable
Viikila J, Lilleberg J, Tierala I, Syvanne M, Kupari M, Salomaa V, et al. Outcome up to one year following different reperfusion strategies in acute ST-segment elevation myocardial infarction: the Helsinki-Uusimaa Hospital District registry of ST-Elevation Acute Myocardial Infarction (HUS-STEMI). Eur Heart J Acute Cardiovasc Care. 2013;2(4):371-8.	Not a pharmacoinvasive strategy
Vora A, Holmes D, Rokos I, Roe M, Granger C, French W, et al. Fibrinolytic therapy use among STEMI patients transferred to a primary PCI hospital in the united states: A report from the mission: Lifeline program. J Am Coll Cardiol. 2013;61(10):E156.	Not a pharmacoinvasive strategy
Vora AN, Holmes DN, Rokos I, Roe MT, Granger CB, French WJ, et	Conference papers and

Study	
al. Fibrinolysis use among patients requiring interhospital transfer for ST-segment elevation myocardial infarction care: a report from the US National Cardiovascular Data Registry. JAMA Intern Med. 2015;175(2):207-15.	abstracts where the full paper is unobtainable
Wallace EL, Kotter JR, Charnigo R, Kuvlieva LB, Smyth SS, Ziada KM, et al. Fibrinolytic therapy versus primary percutaneous coronary interventions for ST-segment elevation myocardial infarction in Kentucky: time to establish systems of care? South Med J. 2013;106(7):391-8.	Not a pharmacoinvasive strategy
Wang YB, Fu XH, Gu XS, Geng W, Zhao YJ, Hao GZ, et al. Thrombolysis Followed by Early Percutaneous Coronary Intervention via Transradial Artery Approach in Patients with ST-Segment Elevation Infarction. Acta Cardiol Sin. 2014;30(4):284-91.	Not a pharmacoinvasive strategy
Weirick T, Denktas A, Anderson V, Smalling R. Fibrinolytic acceleration of STEMI treatment coupled with urgent PCI (FAST-PCI) in an urban setting improves infarct vessel patency, decreases ischemic time, and reduces peak biomarker levels without a bleeding penalty. J Am Coll Cardiol. 2009;53(10):A58.	Conference papers and abstracts where the full paper is unobtainable
Welsh RC, Goldstein P, Carvalho A, Ostojic MC, Nanas J, Zheng Y, et al. Impact on clinical outcomes of randomization at community hospitals versus pre-hospital location in STEMI patients: insights from the stream study. Circulation. 2015;132(no pagination).	Conference papers and abstracts where the full paper is unobtainable
Welsh RC, Goldstein P, Sinnaeve P, Ostojic MC, Zheng Y, Danays T, et al. Relationship between community hospital versus pre-hospital location of randomisation and clinical outcomes in ST-elevation myocardial infarction patients: insights from the Stream study. Eur Heart J Acute Cardiovasc Care. 2018;7(6):504-13.	Wrong comparator
Welsh RC, Van De Werf F, Goldstein P, Gershlick AH, Wilcox R, Danays T, et al. Impact of rescue/urgent angiography on outcomes of ST-elevation myocardial infarction: Insights from stream. Circulation. 2013;128(22).	Conference papers and abstracts where the full paper is unobtainable
Welsh RC, Van de Werf F, Westerhout CM, Goldstein P, Gershlick AH, Wilcox RG, et al. Outcomes of a pharmacoinvasive strategy for successful versus failed fibrinolysis and primary percutaneous intervention in acute myocardial infarction (from the STrategic Reperfusion Early After Myocardial Infarction study). American journal of cardiology. 2014;114(6):811-9.	Wrong comparator
Yang JG, Pi L, Song L, Sun YH, Hu DY. Impact of therapy options on in-hospital and three-year outcome of patients with ST-elevation myocardial infarction in Beijing. Chinese journal of cardiology. 2013;41(6):474-9.	Not a pharmacoinvasive strategy
Zeymer U, Arntz HR, Dirks B, Ellinger K, Genzwürker H, Nibbe L, et al. Reperfusion rate and inhospital mortality of patients with ST segment elevation myocardial infarction diagnosed already in the prehospital phase: Results of the German Prehospital Myocardial Infarction Registry (PREMIR). Resuscitation. 2009;80(4):402-6.	Not a pharmacoinvasive strategy
Zyrianov I, Bessonov I, Kuznetsov V, Sapozhnikov S, Takkand A. In-Hospital outcomes of routine early post-thrombolysis percutaneous coronary intervention in acute ST-elevation myocardial infarction. J Am Coll Cardiol. 2014;64(11):B15.	Conference papers and abstracts where the full paper is unobtainable

Appendix 7 — Meta-regression (RQ3)

A7.1: Total PCI hospital volume

Figure A.1 Total PCI hospital volume vs. study period

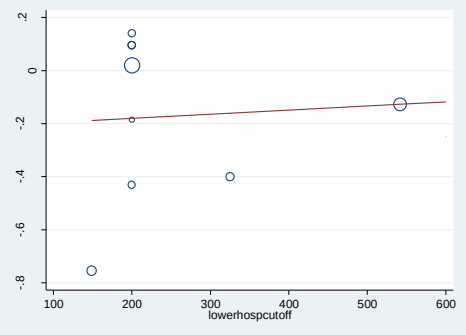


Median study period: Coefficient = 0.0094368 (95% CI -0.051-0.070)

Constant: Coefficient = -19.13016

P (for moderator effect) = 0.72 N=9 observations

Figure A.2 Total hospital PCI volume vs. Lower cut-off value

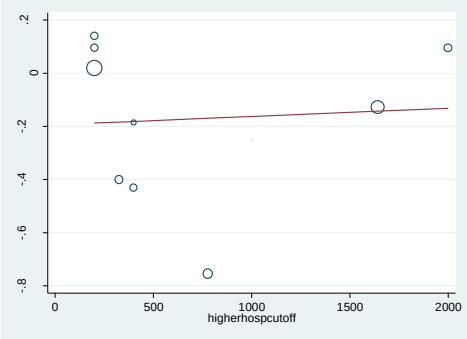


Lower hospital cut-off: Coefficient = 0.0001548 (95% CI -0.0021 - 0.0024)

Constant: Coefficient = -.2109178

P (for moderator effect) = 0.874 N=9 observations

Figure A.3 Total hospital PCI volume vs. Higher cut-off point

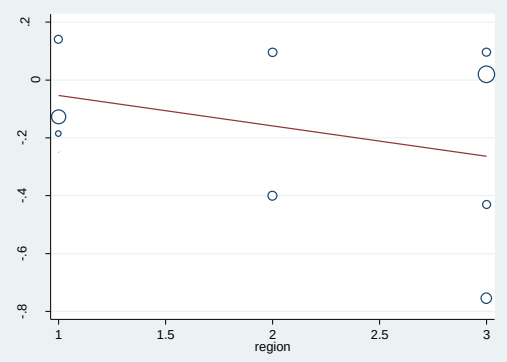


Higher hospital cut-off: Coefficient = 0.0000311 (95% CI -0.00040 - 0.00043)

Constant: Coefficient = -.1938815

P (for moderator effect) = 0.861 N=9 observations

Figure A.4 Total hospital PCI volume vs. Region



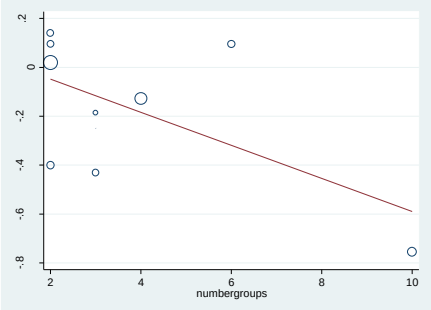
1 – North America; 2 – Europe; 3 - Asia

Region: Coefficient = -.1052743 (95% CI -0.3890 - 0.1785)

Constant: Coefficient = .0522602

P (for moderator effect) =0.409 N=9 observations

Figure A.5 Total hospital PCI volume vs. Number of groupings

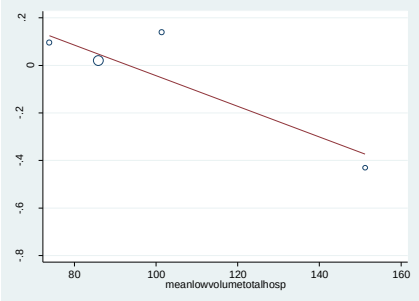


Number of groupings: Coefficient
= -.0676884 (95% CI -0.1474 - 0.01209)

Constant: Coefficient = .0869867

P (for moderator effect) = 0.085 N=9 observations

Figure A.6 Total hospital PCI volume vs. Mean volume of lowest group

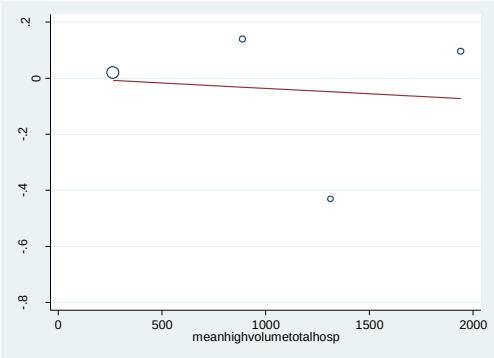


Mean volume of lowest group: Coefficient
= -0.0064580 (95% CI -0.016909 - 0.0040594)

Constant: Coefficient = 0.6020166

P (for moderator effect) = 0.118 N=4 observations

Figure A.7 Total hospital PCI volume vs. Mean volume of highest group



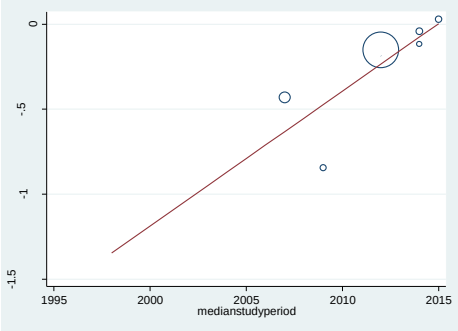
Mean volume of highest group: Coefficient
= -.0000386 (95% CI -0.0011143 - 0.0010371)

Constant: Coefficient
= .0023001

P (for moderator effect) = 0.891 N=4 observations

A7.2: Total PCI operator volume

Figure A.8 Total operator volume vs. Median study period

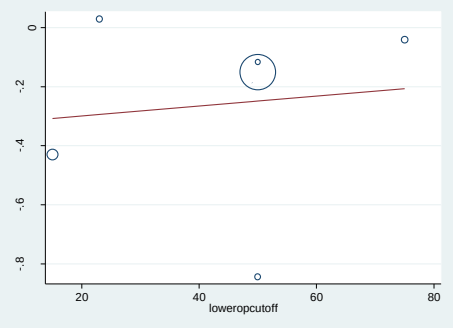


Mean study period: Coefficient = .0793819 (95% CI -0.0041 - 0.1628)

Constant: Coefficient = -159.9514

P (for moderator effect) = 0.057 N=6 observations

Figure A.9: Total operator volume vs. Lowest volume cut-off value

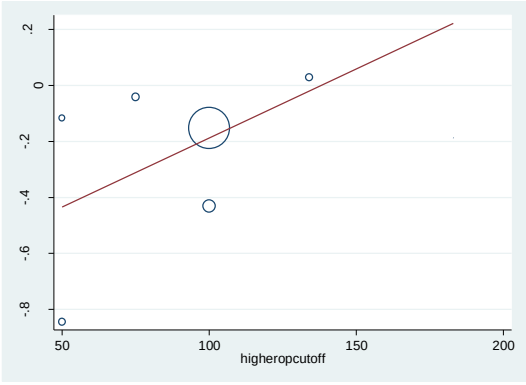


Lowest cut off value: Coefficient = .001687 (95% CI -.0189 - 0.0222)

Constant: Coefficient = -.3329733

P (for moderator effect) = 0.831 N=6 observations

Figure A.10 Total operator volume vs. Highest volume cut-off value

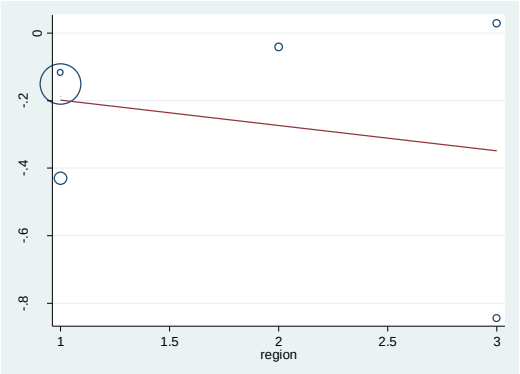


Highest cut off value: Coefficient = .0049357 (95% CI -0.0071 - 0 .0169)

Constant: Coefficient = -.6817413

P (for moderator effect) = 0.319 N=6 observations

Figure A.11 Total operator volume vs. Region



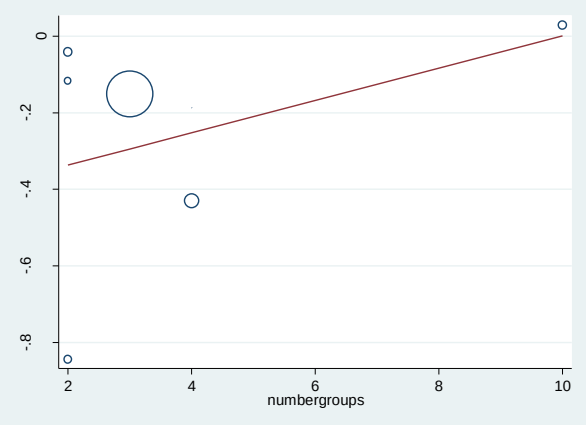
1 – North America; 2 – Europe; 3 - Asia

Region: Coefficient = -.0751226 (95% CI -0.5218 - 0.3716)

Constant: Coefficient = -.1228976

P (for moderator effect) = 0.665 N=6 observations

Figure A.12 Total operator volume vs. Number of groupings



Number of groupings: Coefficient = .0423017 (95% CI -0.0909 - 0.1755)

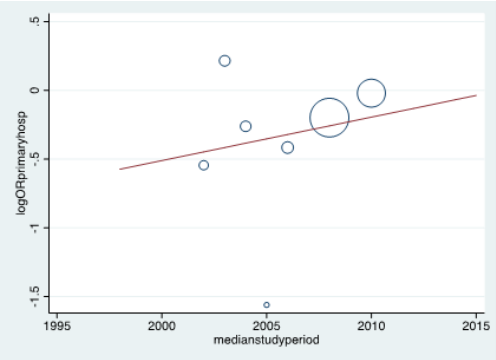
Constant: Coefficient = -.4214382

P (for moderator effect) = 0.88 N=6 observations

Insufficient observations to conduct meta-regression for mean number in lowest and highest groupings

A7.3: Primary PCI hospital volume

Figure A.13 Primary PCI hospital volume vs. Median study period

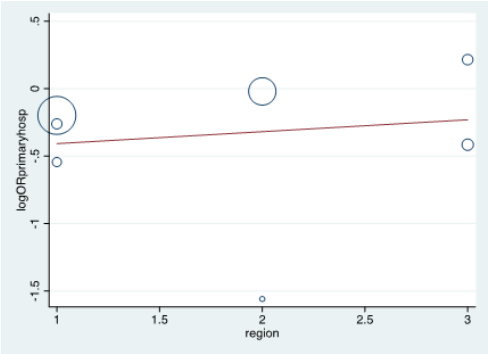


Mean study period: Coefficient
= 0.0315732 (95% CI -0.1642635- 0.22741)

Constant: Coefficient = -63.657

P (for moderator effect) = 0.696 N=7 observations

Figure A.14 Primary PCI hospital volume vs. Region



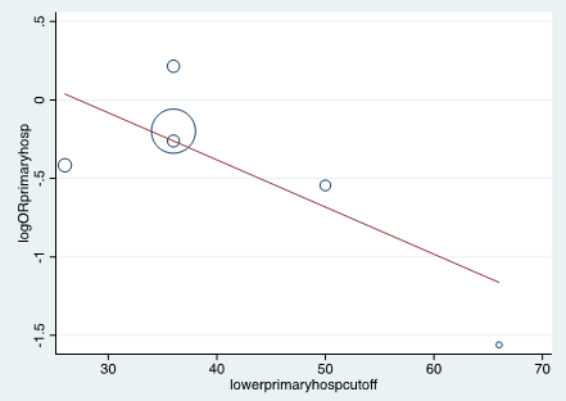
1 – North America; 2 – Europe; 3 - Asia

Region: Coefficient
= 0.0886652 (95% CI -0.5410 - 0.7183)

Constant: Coefficient = -0.4965279

P (for moderator effect) = 0.732 N=7 observations

Figure A.15 Primary hospital volume vs. Lowest volume cut-off value

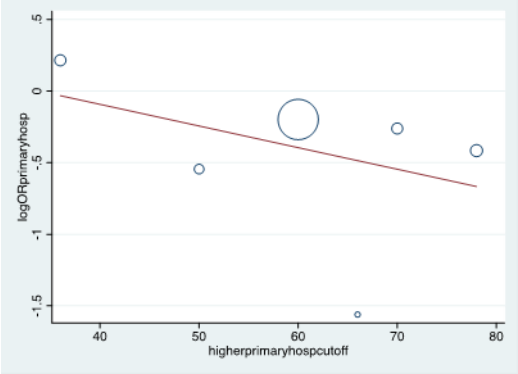


Lowest Volume Cut off value: Coefficient
= -0.030021 (95% CI -0.0686195 - 0.0085775)

Constant: Coefficient = 0.8189288

P (for moderator effect) = 0.097 N=6 observations

Figure A.16 Primary hospital volume vs. Highest volume group cut-off

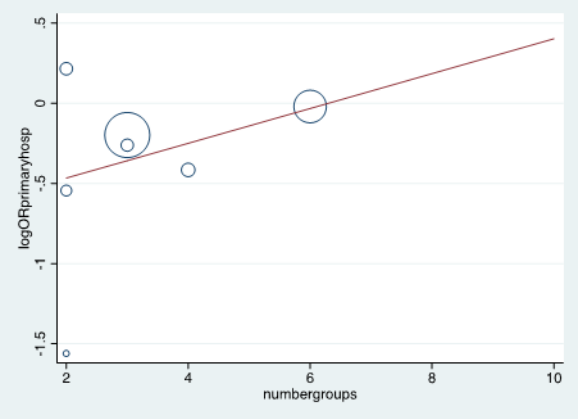


Highest Volume Cut off value: Coefficient
= -0.0151059 (95% CI -0.0589067 - 0.028695)

Constant: Coefficient = 0.5115493

P (for moderator effect) = 0.393 N=6 observations

Figure A.17 Primary PCI hospital volume vs. Number of groupings

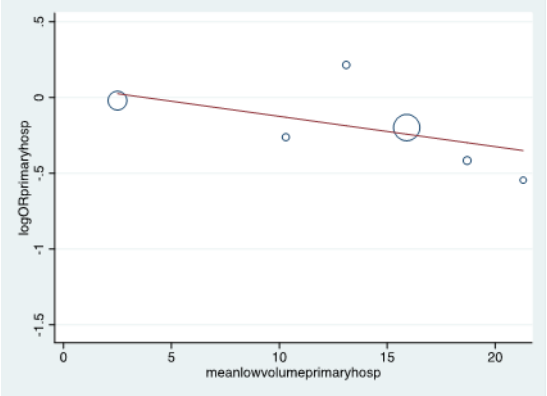


Number of groups: Coefficient = 0.108614 (95% CI -0.2535 - 0.4708)

Constant: Coefficient = -0.6840801

P (for moderator effect) = 0.476 N=7 observations

Figure A.18 Primary PCI hospital volume vs. Mean lowest volume group

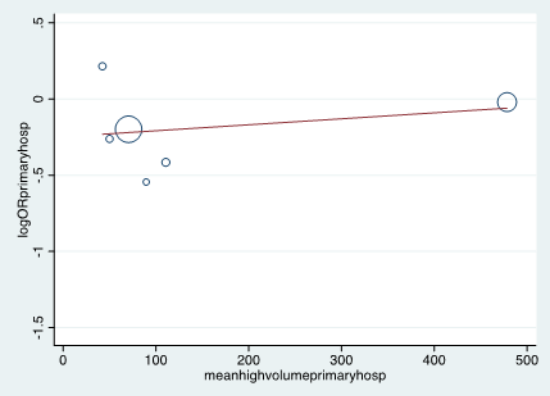


Mean lowest volume group: Coefficient = -0.0199315 (95% CI -0.0531 - 0 .0132)

Constant: Coefficient = 0.0750286

P (for moderator effect) = 0.171 N=6 observations

Figure A.19 Primary PCI hospital vs. Mean volume of highest group



Mean volume of highest group: Coefficient = 0.0003919 (95% CI -0.0014 - 0 .0022)

Constant: Coefficient = -0.2474036

P (for moderator effect) = 0.574 N=6 observations

Appendix 8 — Sensitivity and subgroup analyses

This section includes the outputs of the extensive sensitivity analyses carried out as part of the analyses undertaken for RQ3. Individual analyses use a variety of methodologies (for example, fixed effect or random effects, weighting estimators and treatment effect measures) depending on the context of the data. Forest plots are presented for completeness. Caution must be applied in interpreting the analyses due to the quantity and quality of underlying evidence.

A8.1 Total PCI Hospital Volume (RQ3)

Figure A.20: Sensitivity analysis: Removing Qian et al.

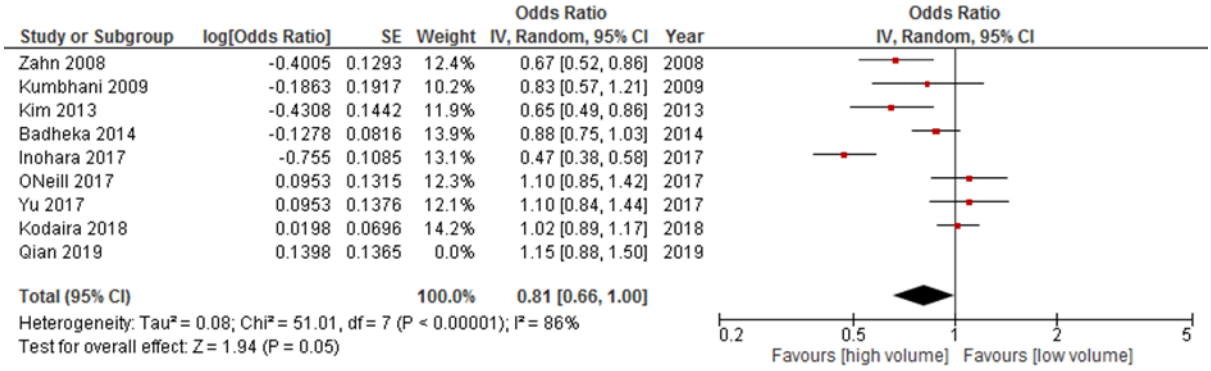


Figure A.21: Sensitivity analysis: Removing Zahn et al

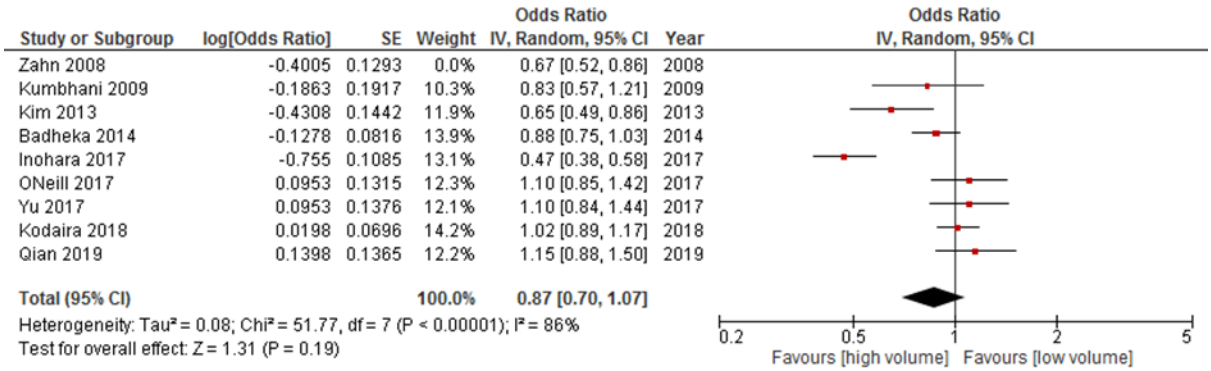


Figure A.22: Sensitivity analysis: Removing Kumbhani et al.

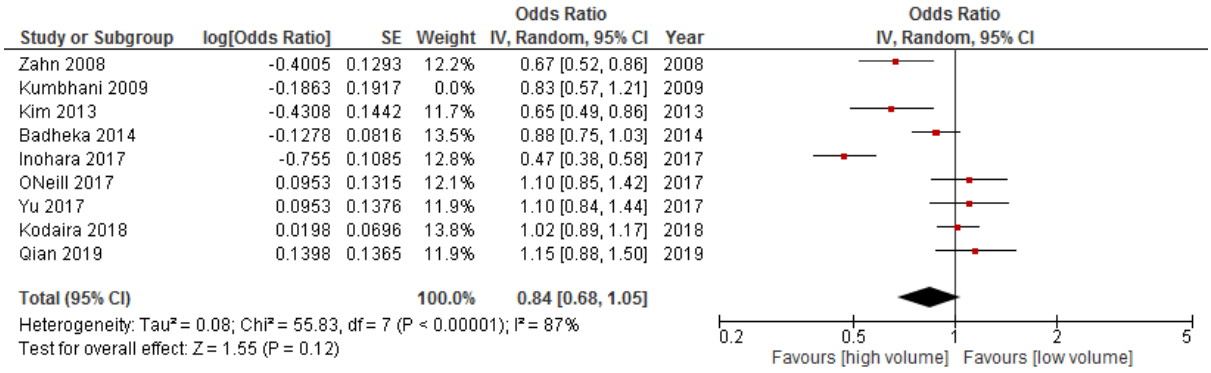


Figure A.23: Sensitivity analysis: Removing Kim et al.

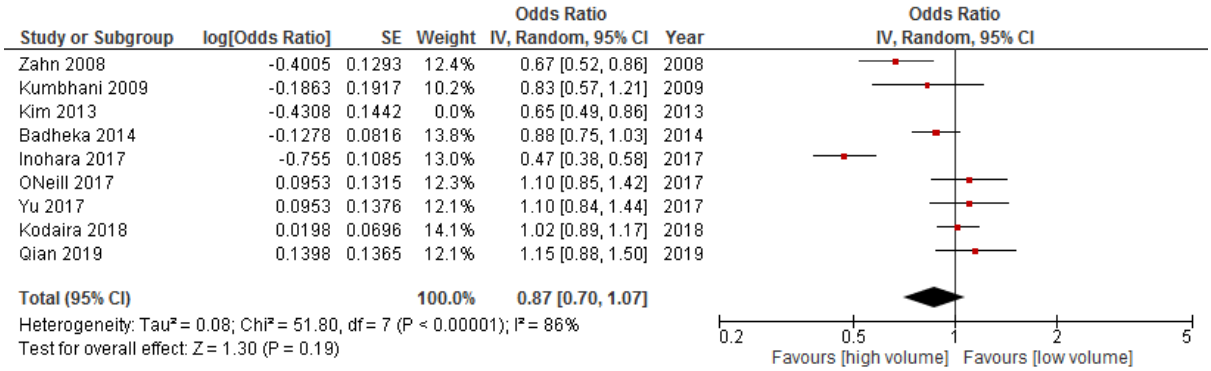


Figure A.24: Sensitivity analysis: Removing Badheka et al.

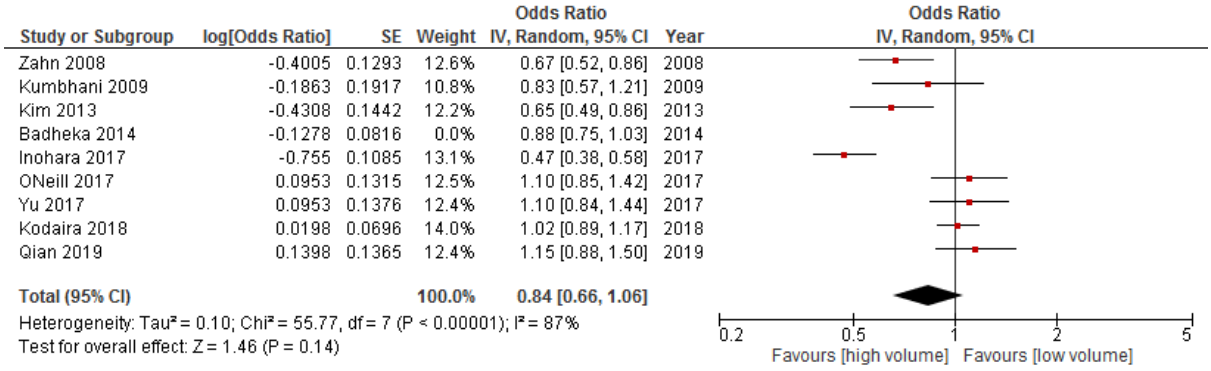


Figure A.25: Sensitivity analysis: Removing Inohara et al.

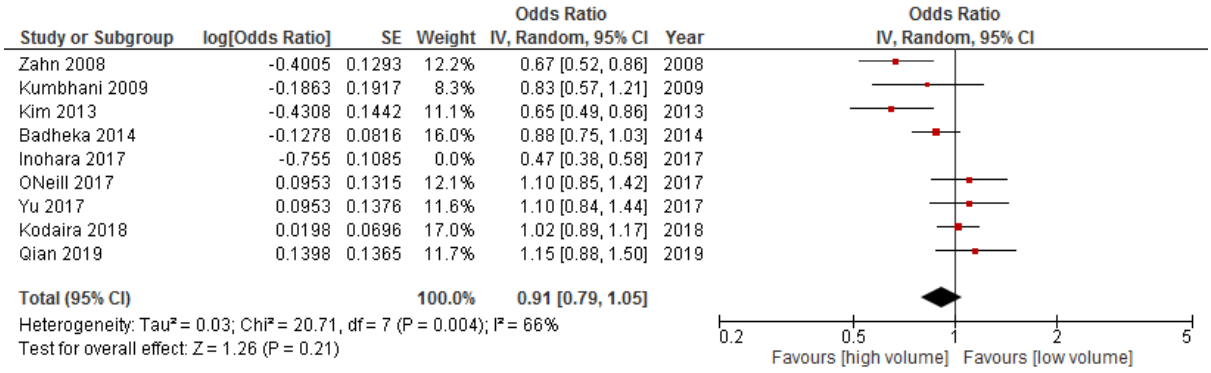


Figure A.26: Sensitivity analysis: Removing Yu et al.

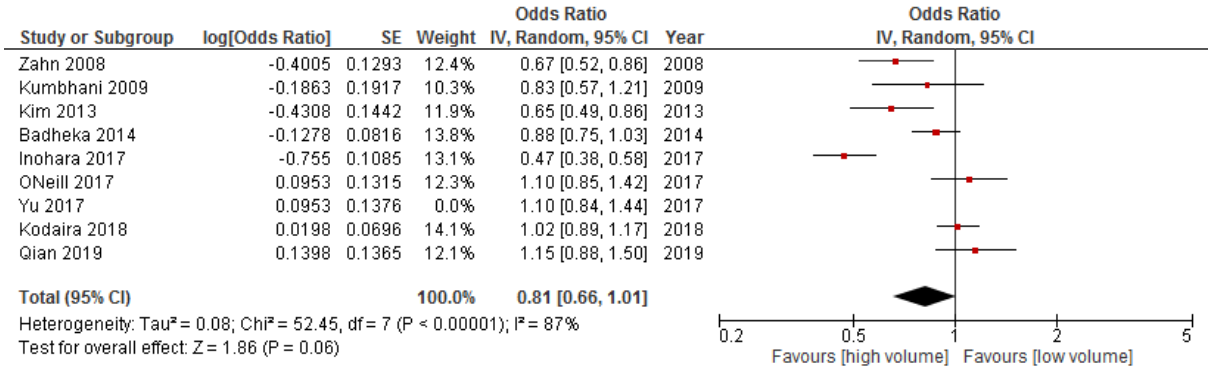


Figure A.27: Sensitivity analysis: Removing Kodaira et al.

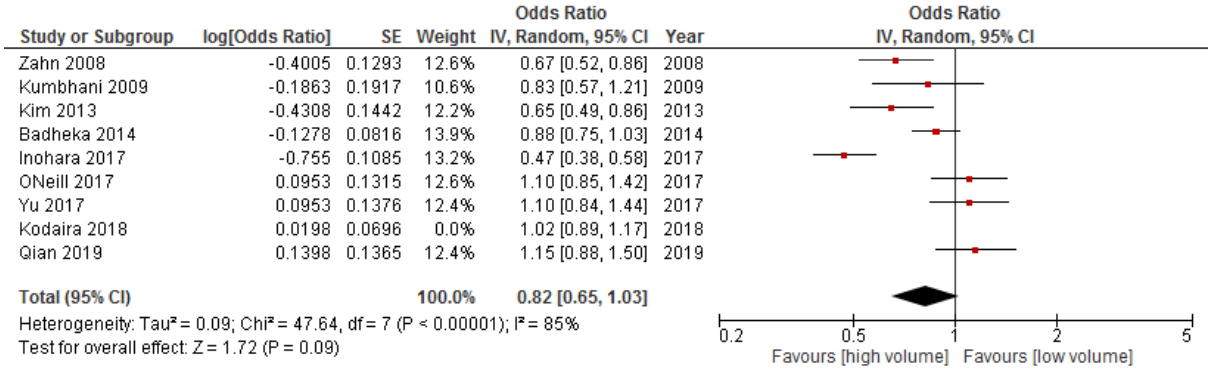


Figure A.28: Sensitivity analysis: Removing O'Neill et al.

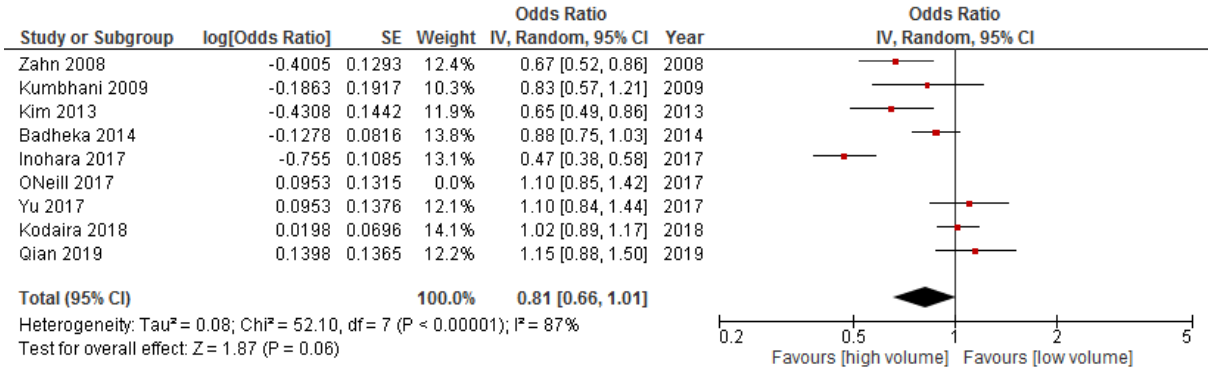


Figure A.29: Sensitivity analysis: Alternative thresholds for Zahn et al. (</> 200 PCI)

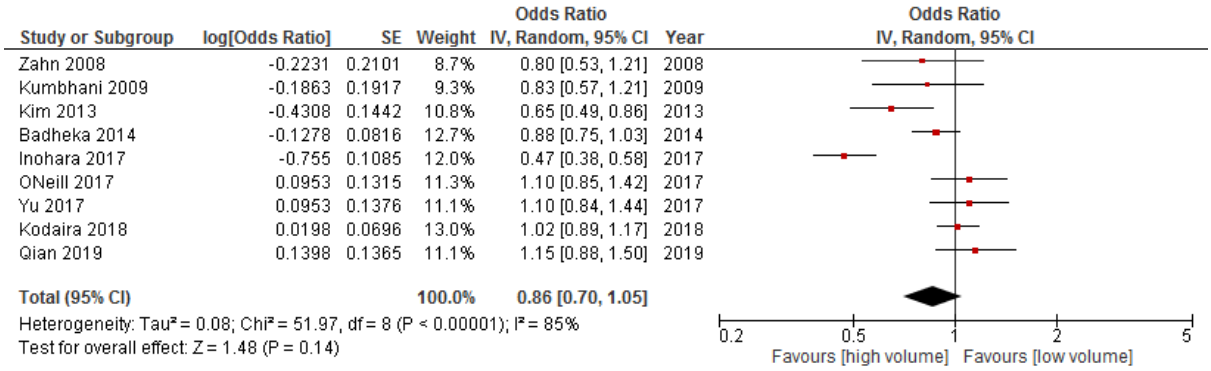


Figure A.30: Sensitivity analysis: Alternative thresholds for Zahn et al. (</> 400 PCI)

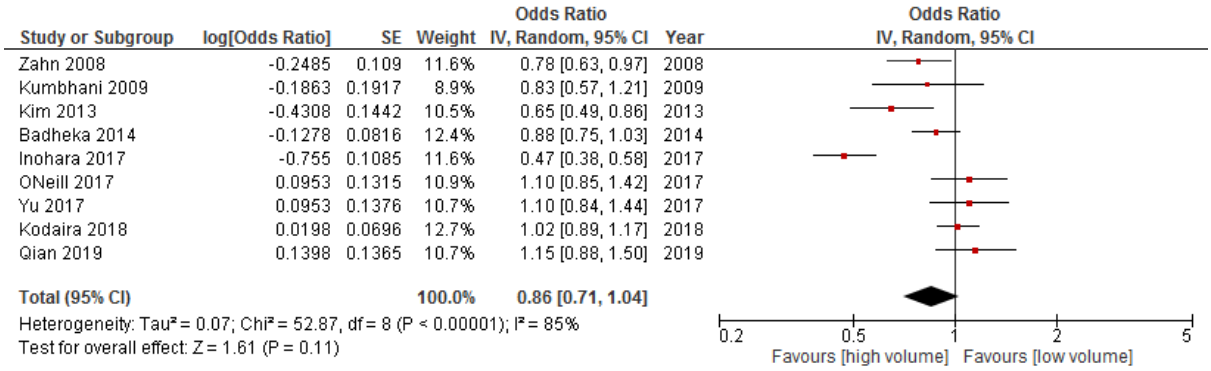


Figure A.31: Sensitivity analysis: Alternative thresholds for Yu et al. (threshold calculated via K-means)

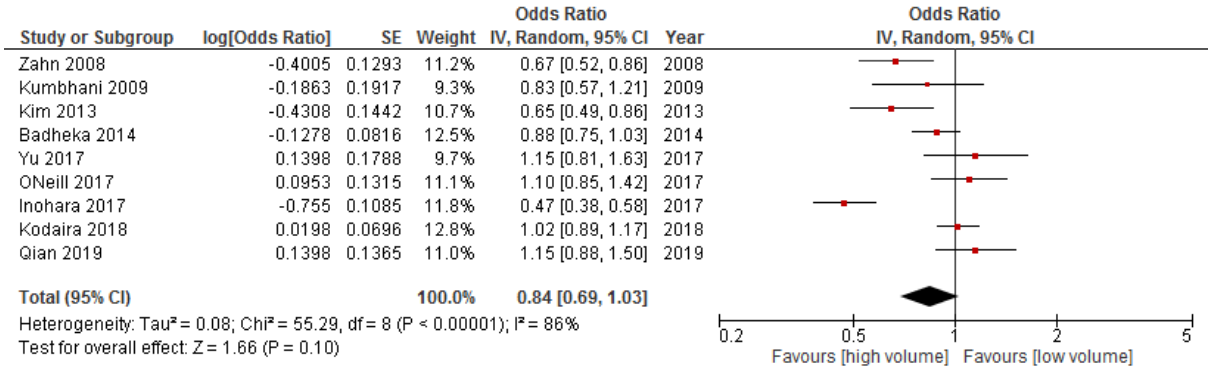


Figure A.32: Sensitivity analysis: Alternative thresholds for Yu et al. (threshold calculated via GAM method)

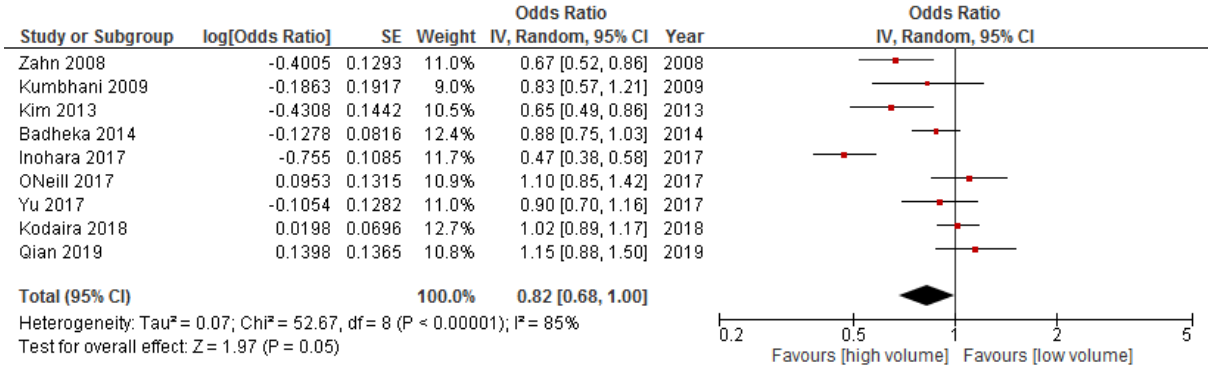


Figure A.33: Sensitivity analysis: Alternative thresholds for Qian et al. (</> 400 PCI)

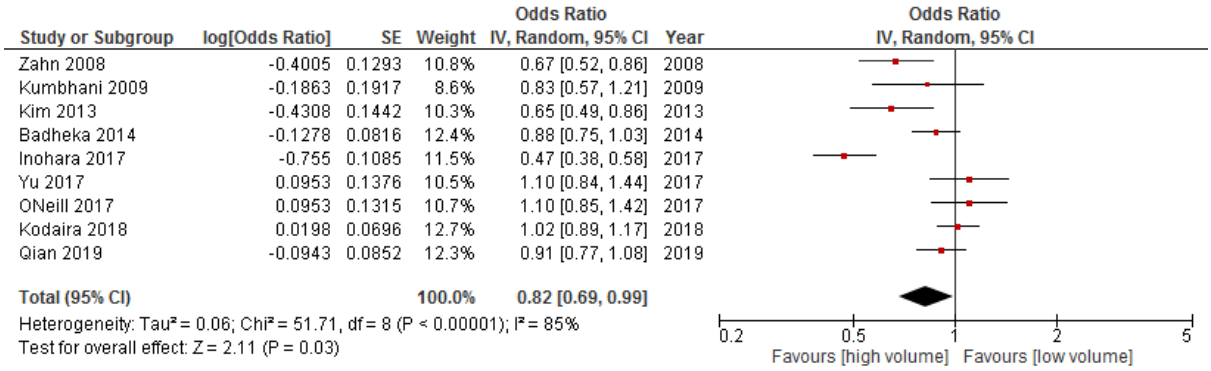


Figure A.34: Sensitivity analysis: Alternative thresholds for Qian et al. (</> 600 PCI)

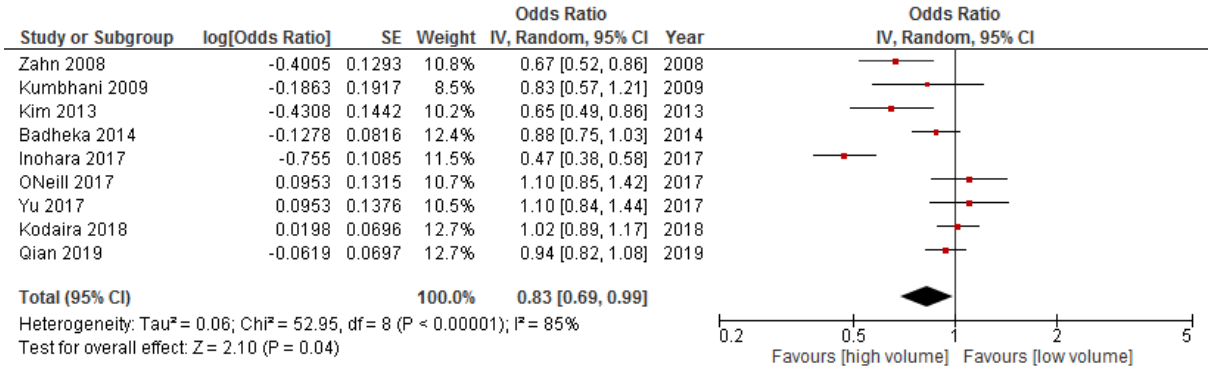


Figure A.35: Sensitivity analysis: Alternative thresholds for Qian et al. (</> 800 PCI)

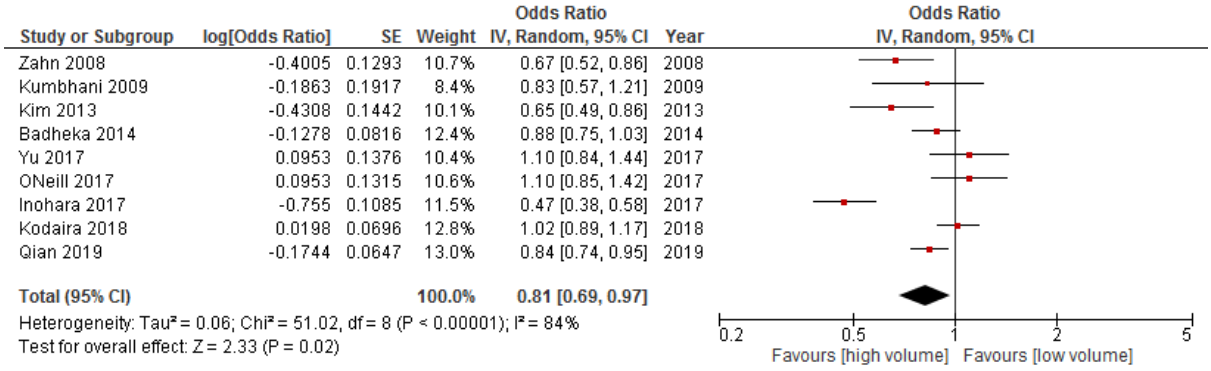


Figure A.36: Sensitivity analysis: Alternative thresholds for Qian et al. (</> 1,000 PCI)

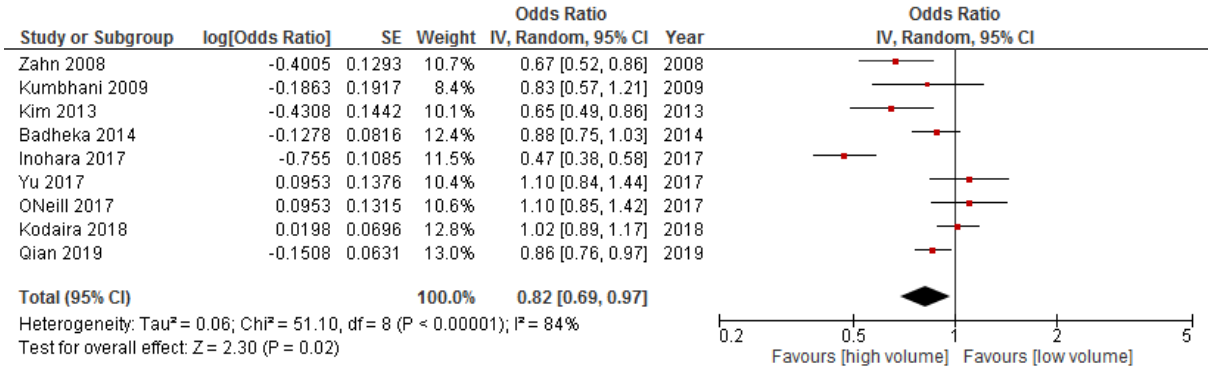


Figure A.37: Subgroup analysis: Risk of bias

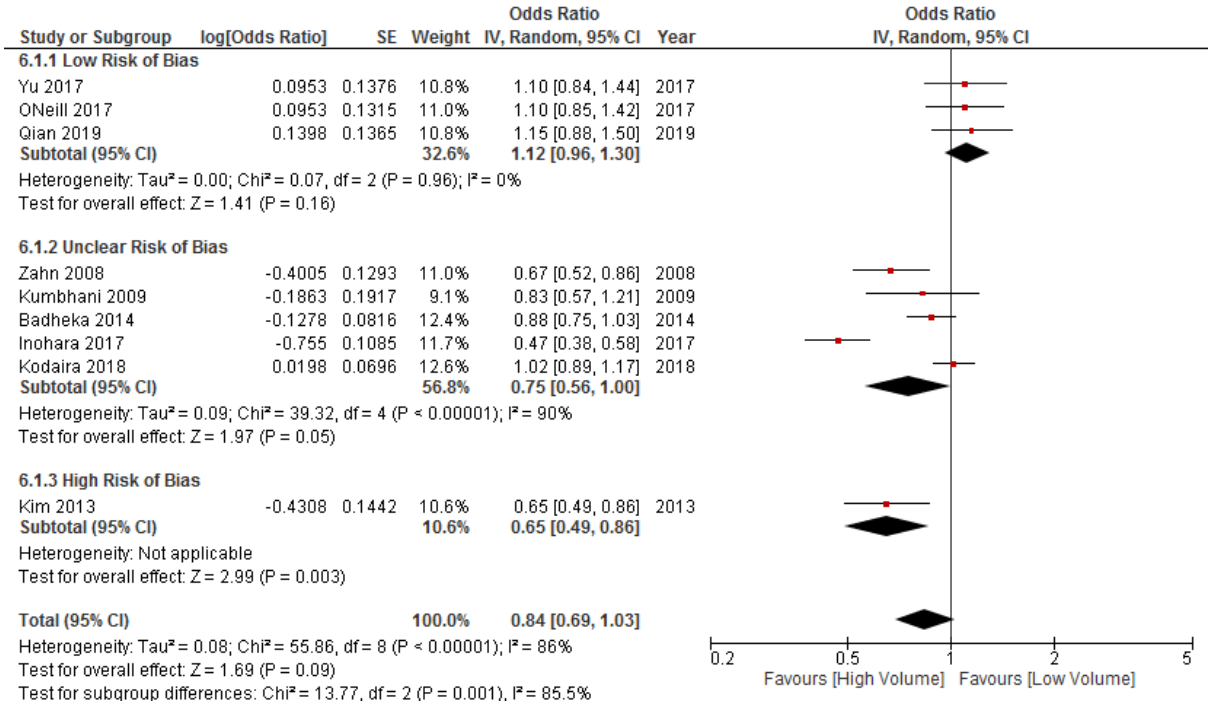


Figure A.38: Subgroup analysis: Region

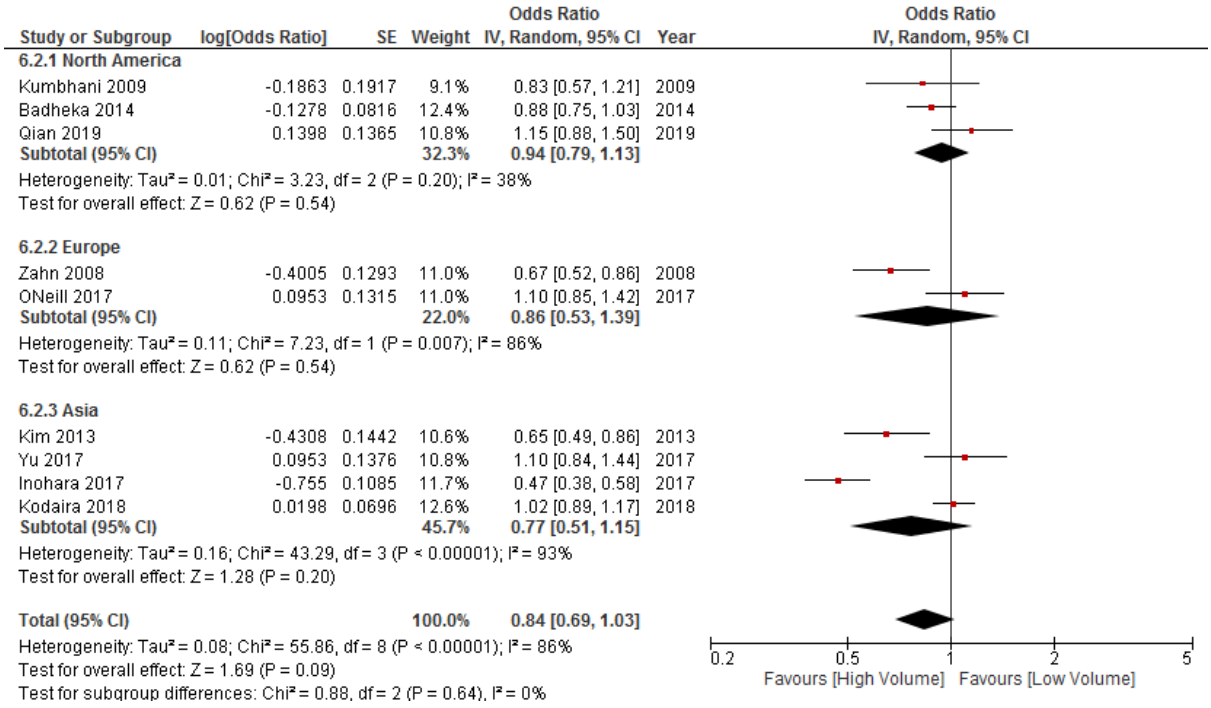


Figure A.39: Subgroup analysis: Completeness of case-mix adjustment

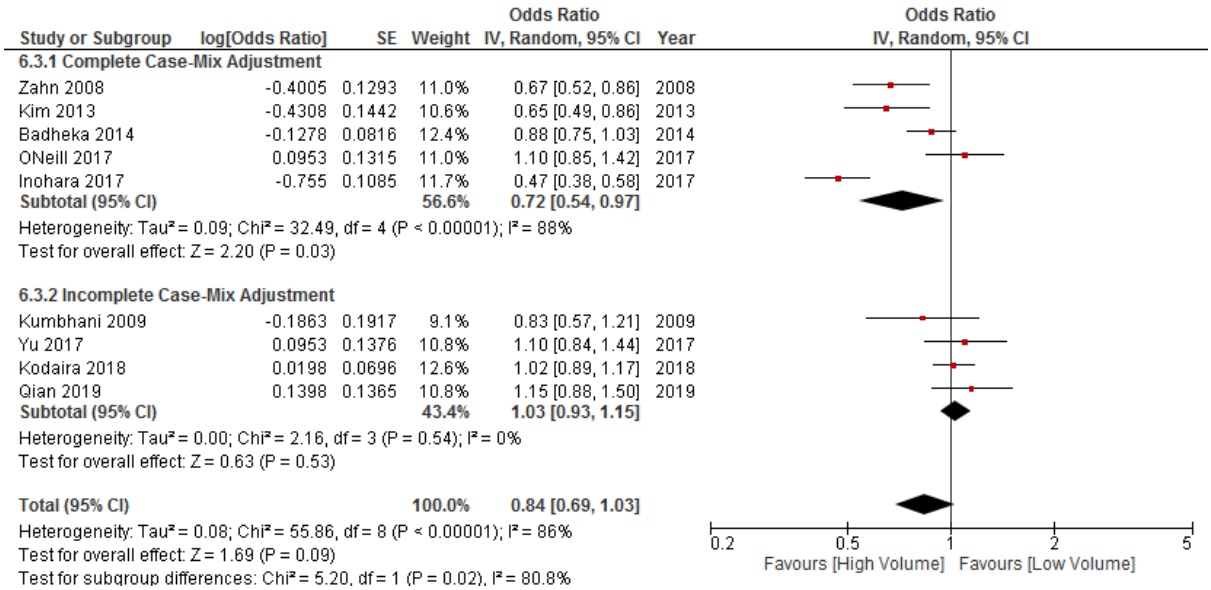


Figure A.40: Subgroup analysis: Definition of a low-volume hospital

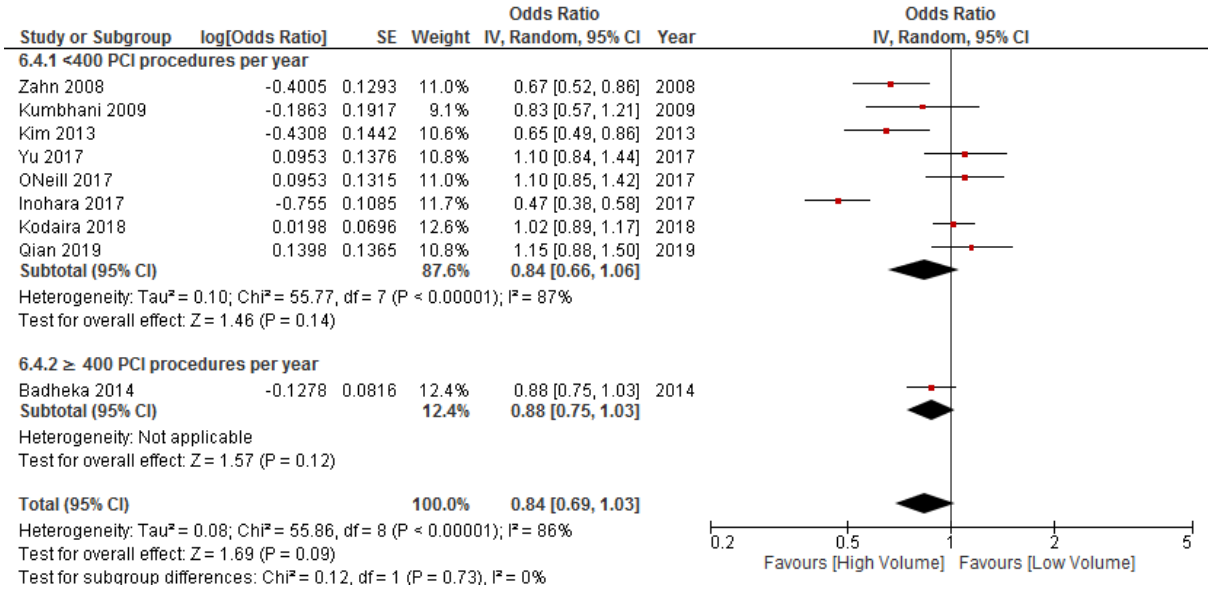


Figure A.41: Subgroup analysis: Study period

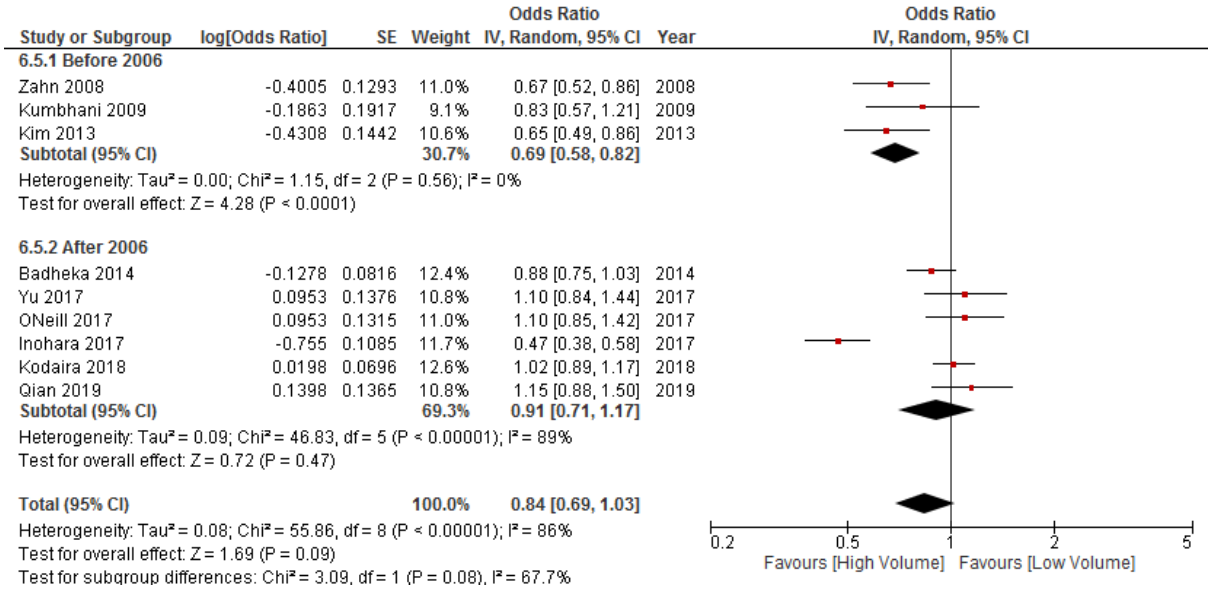
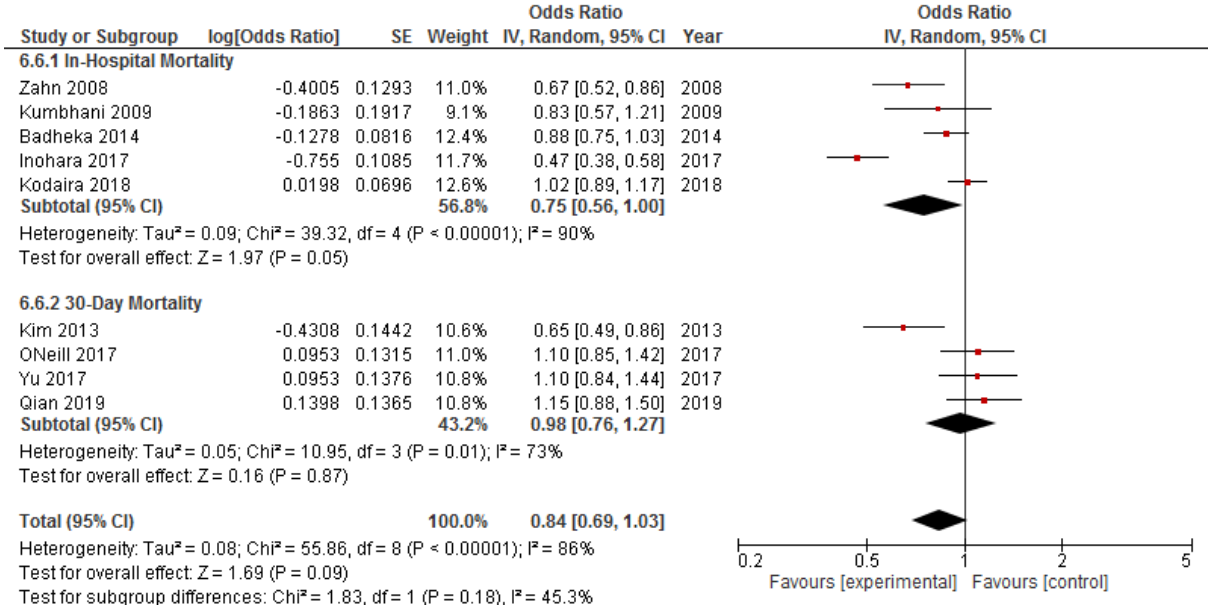


Figure A.42: Subgroup analysis examining the distribution of pooled effect sizes according to the mortality outcome used



A8.2 Total PCI Operator Volume (RQ3)

Figure A.43: Sensitivity analysis: Removing Badheka et al.

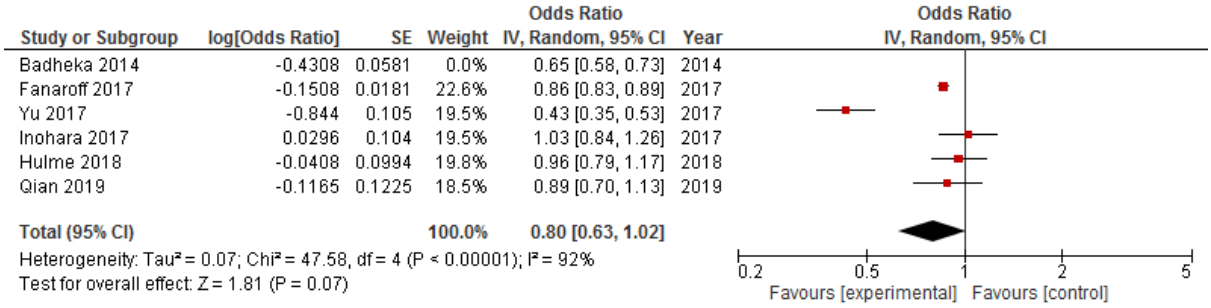


Figure A.44: Sensitivity analysis: Removing Yu et al.

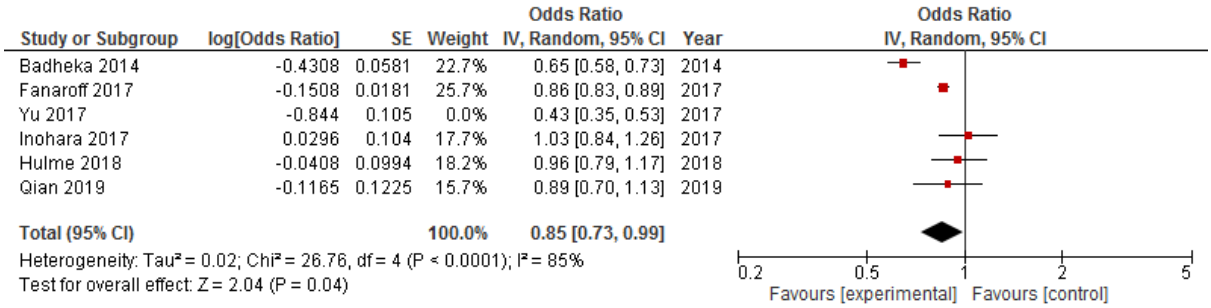


Figure A.45: Sensitivity analysis: Removing Inohara et al.

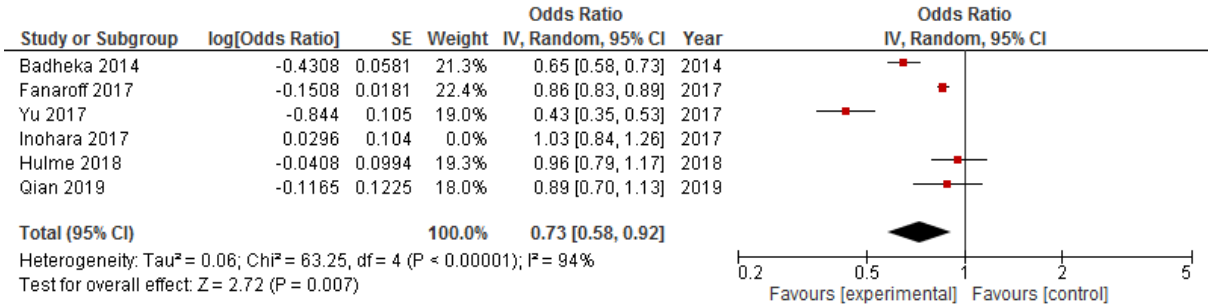


Figure A.46: Sensitivity analysis: Removing Fanaroff et al.

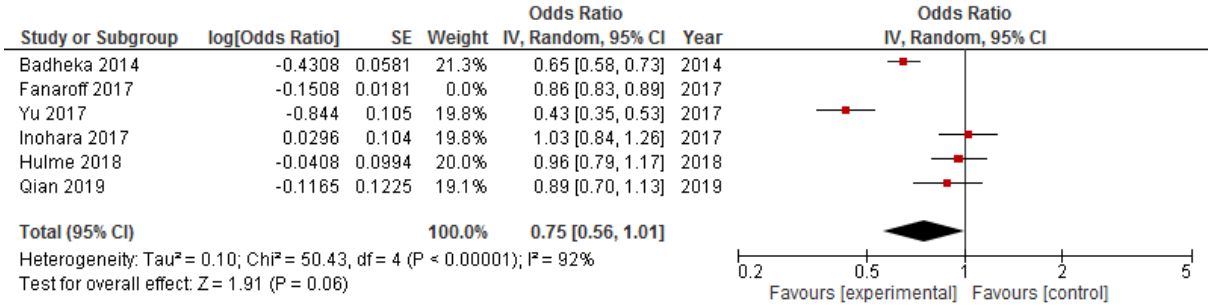


Figure A.47: Sensitivity analysis: Removing Hulme et al.

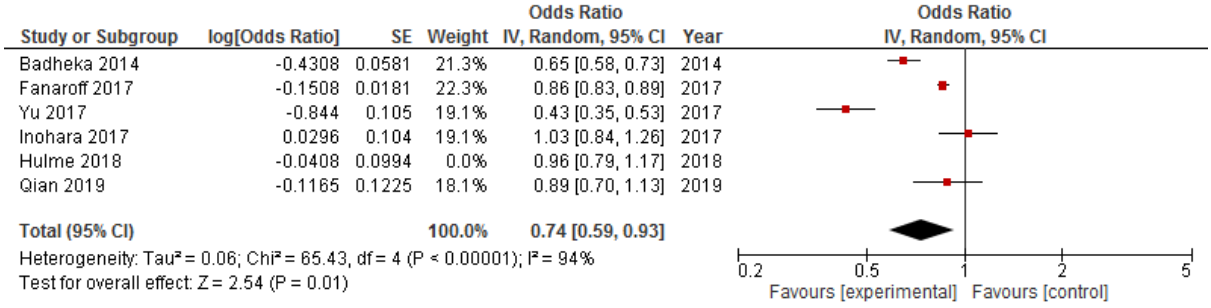


Figure A.48: Sensitivity analysis: Removing Qian et al.

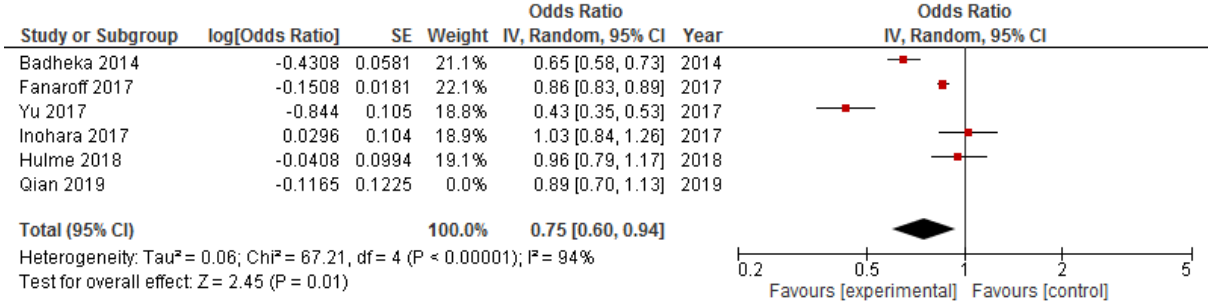


Figure A.49: Subgroup analysis: Risk of bias

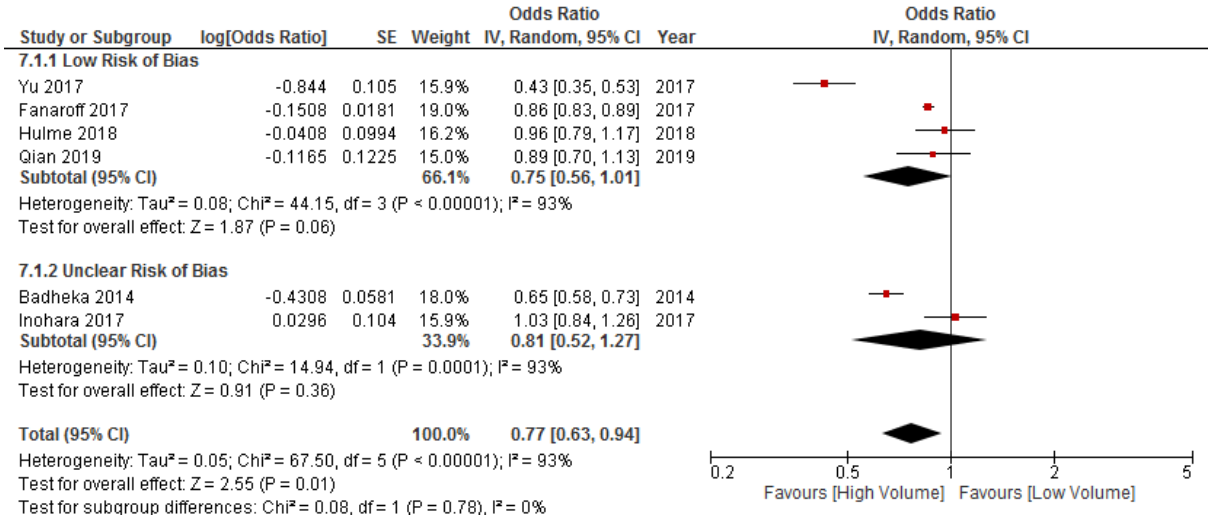


Figure A.50: Subgroup analysis: Region

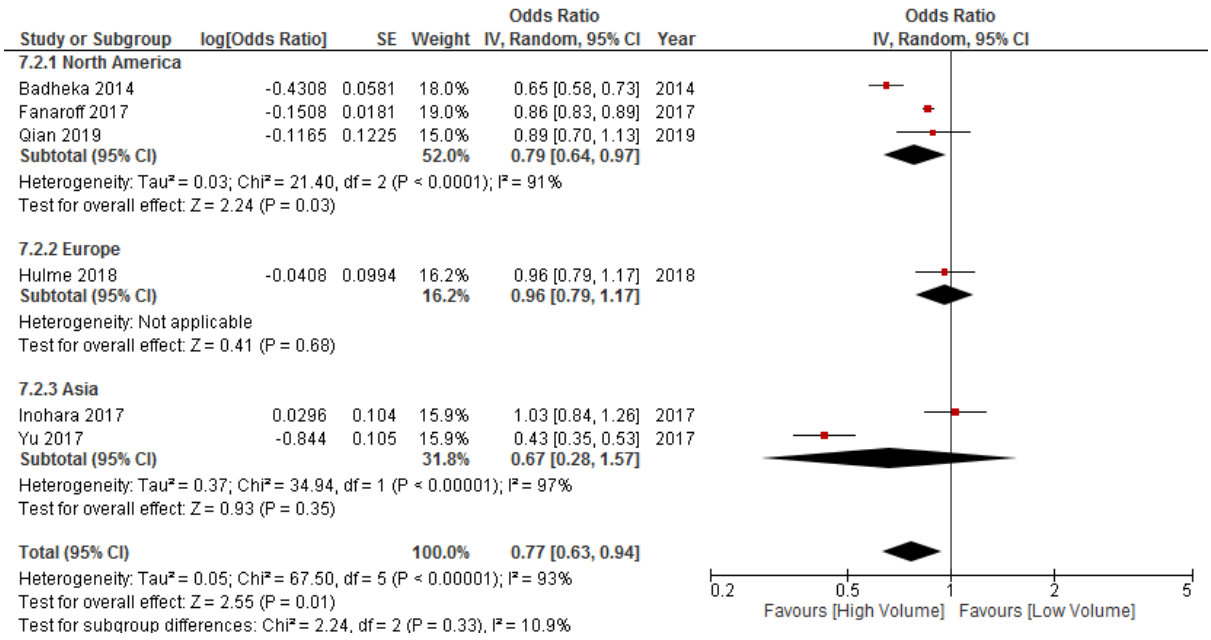


Figure A.51: Subgroup analysis: Completeness of case-mix adjustment

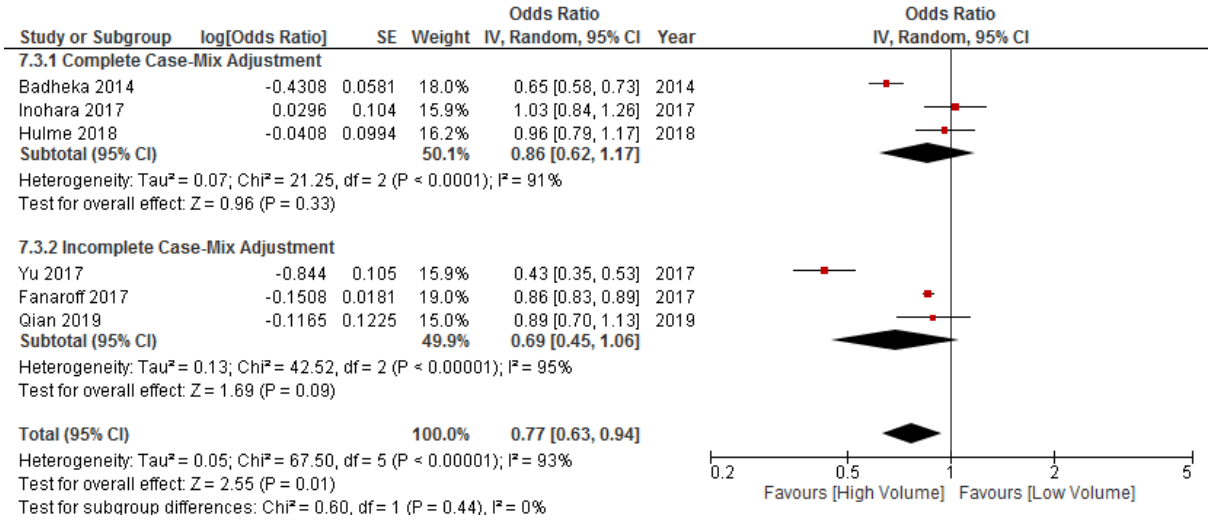


Figure A.52: Subgroup analysis: Definition of low-volume hospital

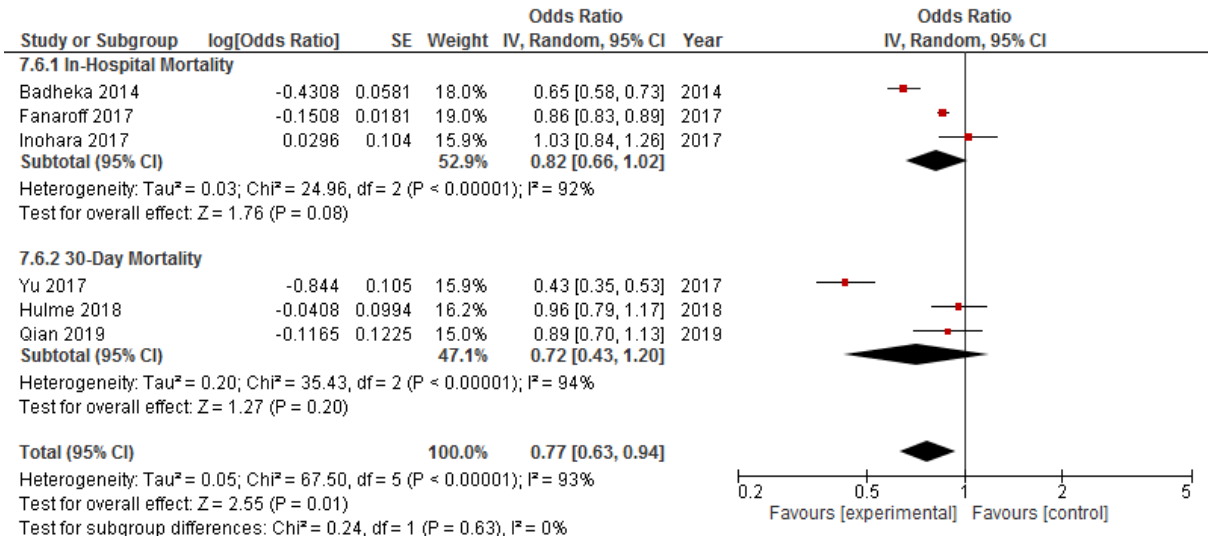


Figure A.53: Sensitivity analysis (alternative thresholds calculated for Yu et al. via k-means)

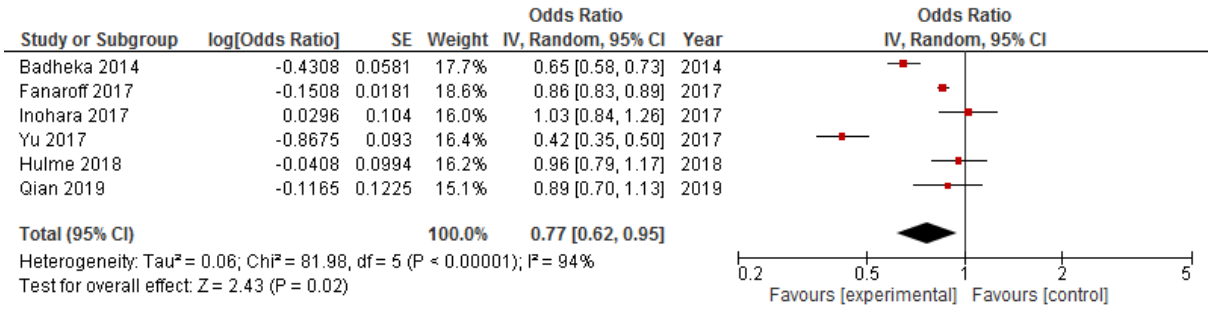


Figure A.54: Sensitivity Analysis (alternative thresholds calculated for Yu et al. via GAM method)

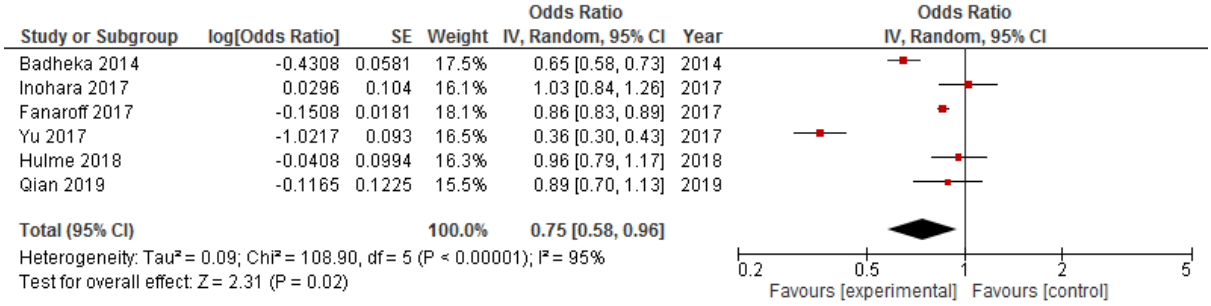


Figure A.55: Sensitivity analysis (alternative thresholds calculated for Hulme et al. as </> 50 PCI procedures per year)

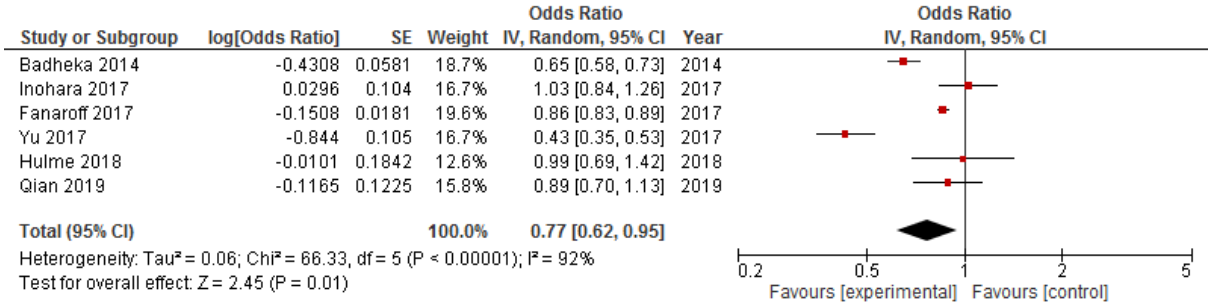


Figure A.56: Sensitivity analysis (alternative thresholds calculated for Fanaroff et al. as <26 and > 413 PCI procedures per year)

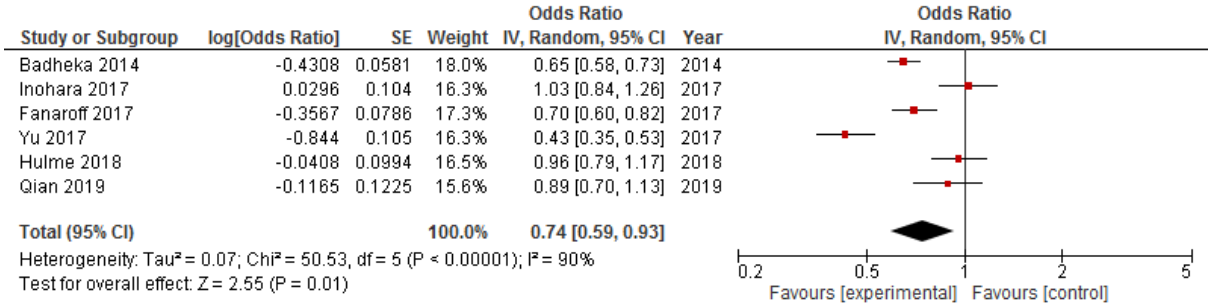
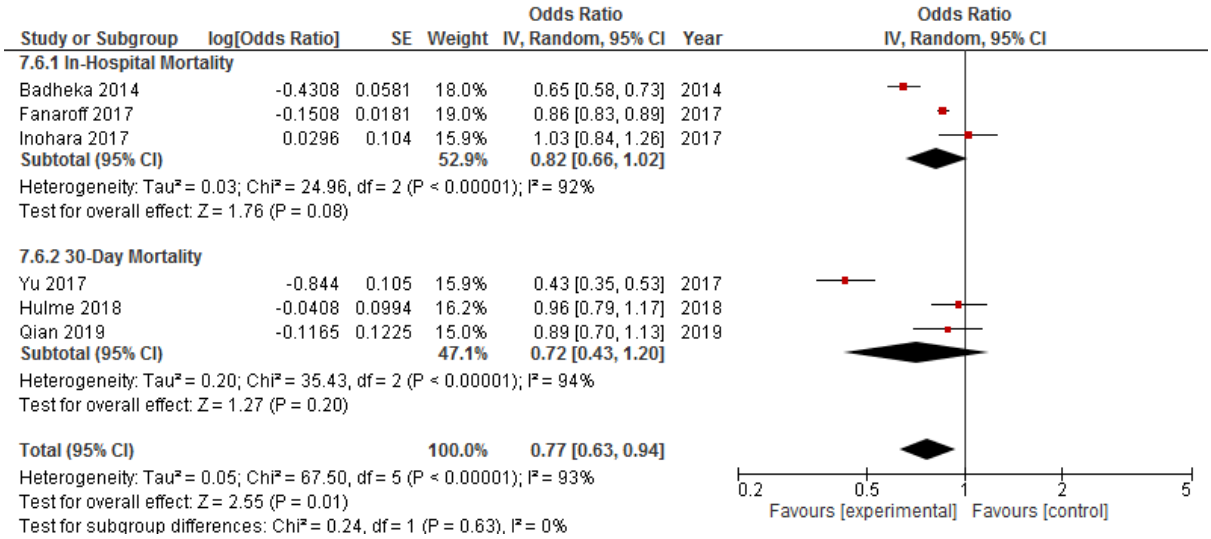


Figure A.57: Subgroup analysis: Examining the distribution of pooled effect sizes according to the mortality outcome used



A8.3 Primary PCI Hospital Volume (RQ3)

Figure A.58: Sensitivity analysis: Removing Shiraishi et al.

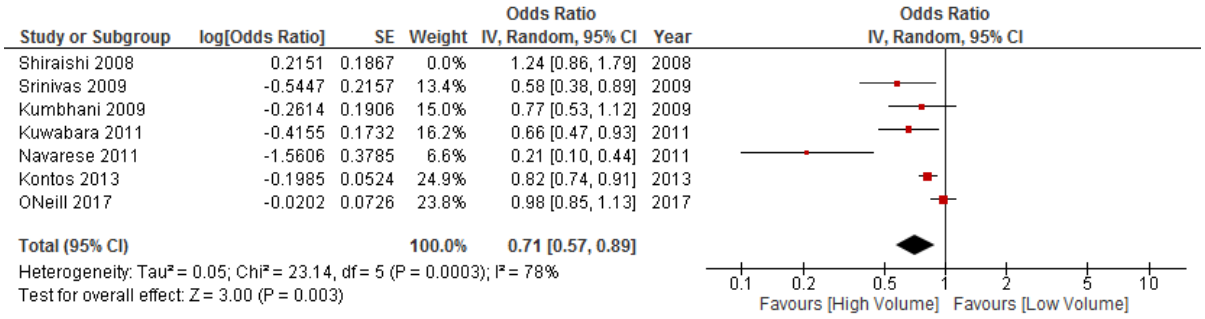


Figure A.59: Sensitivity analysis: Removing Srinivas et al.

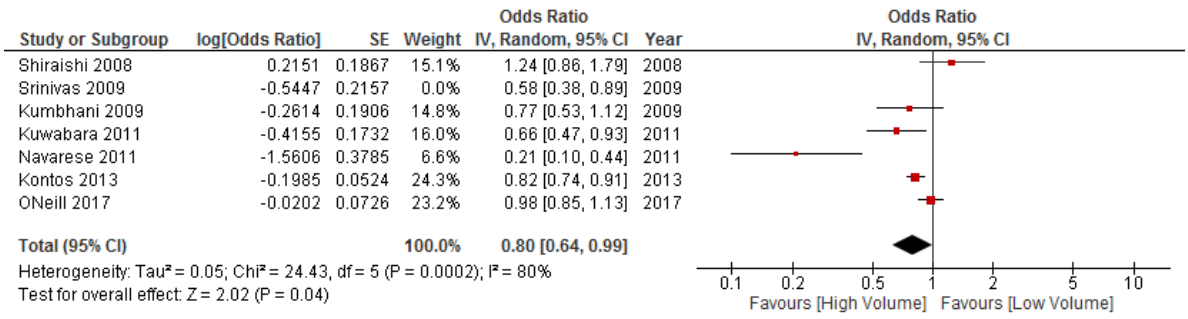


Figure A.60: Sensitivity analysis: Removing Kumbhani et al.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Shiraishi 2008	0.2151	0.1867	15.7%	1.24 [0.86, 1.79]	2008
Srinivas 2009	-0.5447	0.2157	13.9%	0.58 [0.38, 0.89]	2009
Kumbhani 2009	-0.2614	0.1906	0.0%	0.77 [0.53, 1.12]	2009
Kuwabara 2011	-0.4155	0.1732	16.5%	0.66 [0.47, 0.93]	2011
Navarese 2011	-1.5606	0.3785	7.3%	0.21 [0.10, 0.44]	2011
Kontos 2013	-0.1985	0.0524	23.8%	0.82 [0.74, 0.91]	2013
ONeill 2017	-0.0202	0.0726	22.9%	0.98 [0.85, 1.13]	2017
Total (95% CI)			**100.0%**	**0.76 [0.60, 0.96]**	

Heterogeneity: Tau² = 0.06; Chi² = 27.32, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 2.28 (P = 0.02)

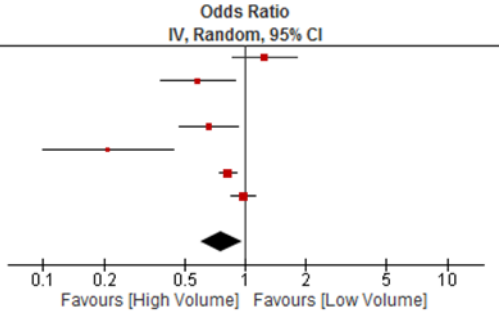


Figure A.61: Sensitivity analysis: Removing Navarese et al.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Shiraishi 2008	0.2151	0.1867	12.1%	1.24 [0.86, 1.79]	2008
Srinivas 2009	-0.5447	0.2157	10.0%	0.58 [0.38, 0.89]	2009
Kumbhani 2009	-0.2614	0.1906	11.8%	0.77 [0.53, 1.12]	2009
Kuwabara 2011	-0.4155	0.1732	13.2%	0.66 [0.47, 0.93]	2011
Navarese 2011	-1.5606	0.3785	0.0%	0.21 [0.10, 0.44]	2011
Kontos 2013	-0.1985	0.0524	27.8%	0.82 [0.74, 0.91]	2013
ONeill 2017	-0.0202	0.0726	25.2%	0.98 [0.85, 1.13]	2017
Total (95% CI)			**100.0%**	**0.84 [0.71, 0.99]**	

Heterogeneity: Tau² = 0.02; Chi² = 13.90, df = 5 (P = 0.02); I² = 64%
Test for overall effect: Z = 2.11 (P = 0.04)

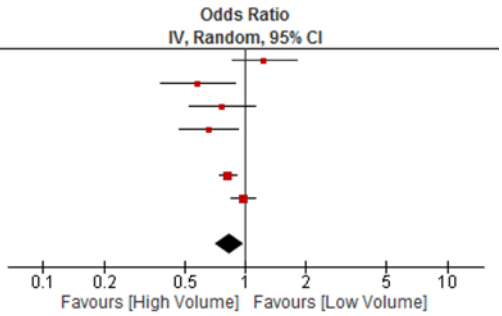


Figure A.62: Sensitivity analysis: Removing Kuwabarra et al.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Shiraishi 2008	0.2151	0.1867	15.7%	1.24 [0.86, 1.79]	2008
Srinivas 2009	-0.5447	0.2157	13.9%	0.58 [0.38, 0.89]	2009
Kumbhani 2009	-0.2614	0.1906	15.4%	0.77 [0.53, 1.12]	2009
Kuwabara 2011	-0.4155	0.1732	0.0%	0.66 [0.47, 0.93]	2011
Navarese 2011	-1.5606	0.3785	7.1%	0.21 [0.10, 0.44]	2011
Kontos 2013	-0.1985	0.0524	24.4%	0.82 [0.74, 0.91]	2013
ONeill 2017	-0.0202	0.0726	23.4%	0.98 [0.85, 1.13]	2017
Total (95% CI)			**100.0%**	**0.78 [0.62, 0.99]**	

Heterogeneity: Tau² = 0.06; Chi² = 25.43, df = 5 (P = 0.0001); I² = 80%
Test for overall effect: Z = 2.08 (P = 0.04)

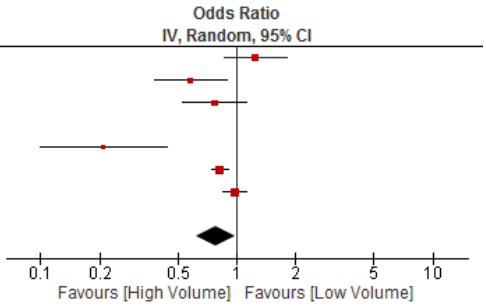


Figure A.63: Sensitivity analysis: Removing Kontos et al.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Shiraishi 2008	0.2151	0.1867	17.3%	1.24 [0.86, 1.79]	2008
Srinivas 2009	-0.5447	0.2157	16.1%	0.58 [0.38, 0.89]	2009
Kumbhani 2009	-0.2614	0.1906	17.1%	0.77 [0.53, 1.12]	2009
Kuwabara 2011	-0.4155	0.1732	17.9%	0.66 [0.47, 0.93]	2011
Navarese 2011	-1.5606	0.3785	10.2%	0.21 [0.10, 0.44]	2011
Kontos 2013	-0.1985	0.0524	0.0%	0.82 [0.74, 0.91]	2013
ONeill 2017	-0.0202	0.0726	21.4%	0.98 [0.85, 1.13]	2017
Total (95% CI)			**100.0%**	**0.72 [0.52, 0.99]**	

Heterogeneity: Tau² = 0.12; Chi² = 26.87, df = 5 (P < 0.0001); I² = 81%
Test for overall effect: Z = 2.03 (P = 0.04)

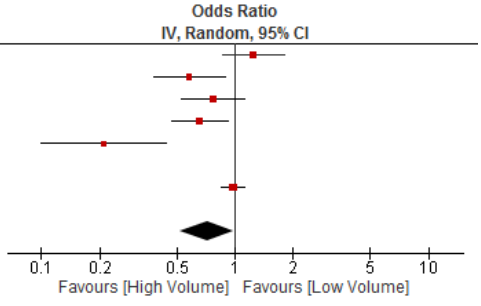


Figure A.64: Sensitivity analysis: Removing O'Neill et al.

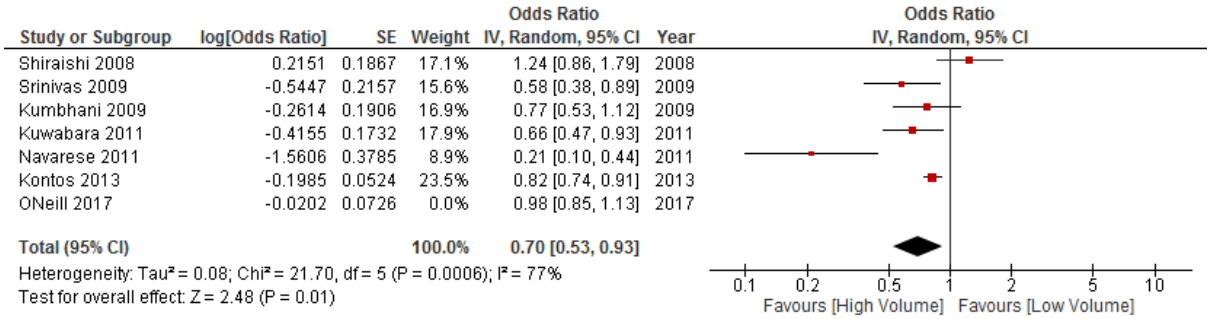


Figure A.65: Sensitivity analysis (alternative thresholds calculated for Srinivas et al. at </> 25 Primary PCI procedures/year)

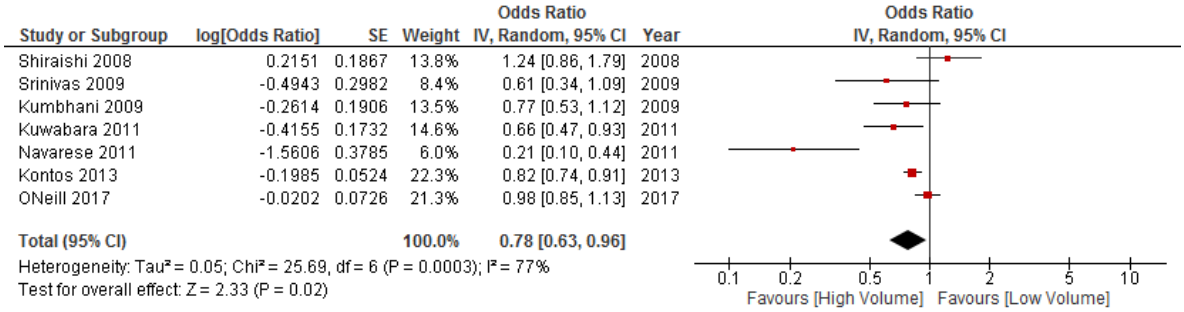


Figure A.66: Sensitivity analysis (alternative thresholds calculated for Srinivas et al. at </> 75 Primary PCI procedures/year)

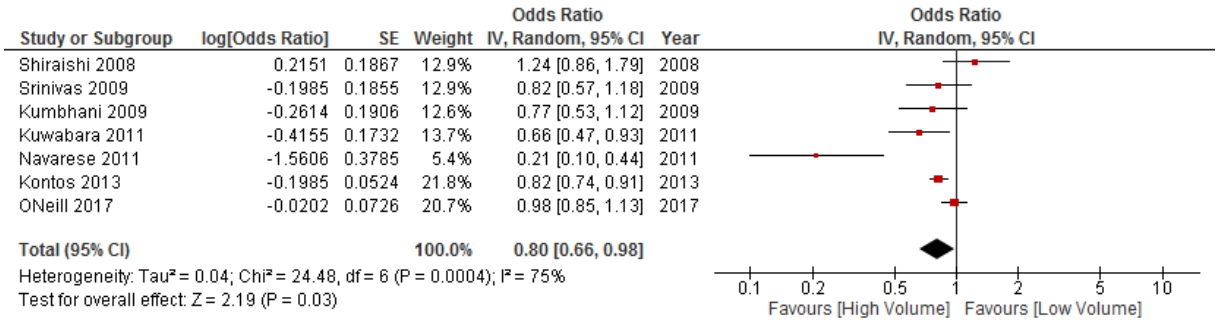


Figure A.67: Sensitivity analysis (alternative thresholds calculated for Kumbhani et al. at < 25 and > 50 Primary PCI procedures/year)

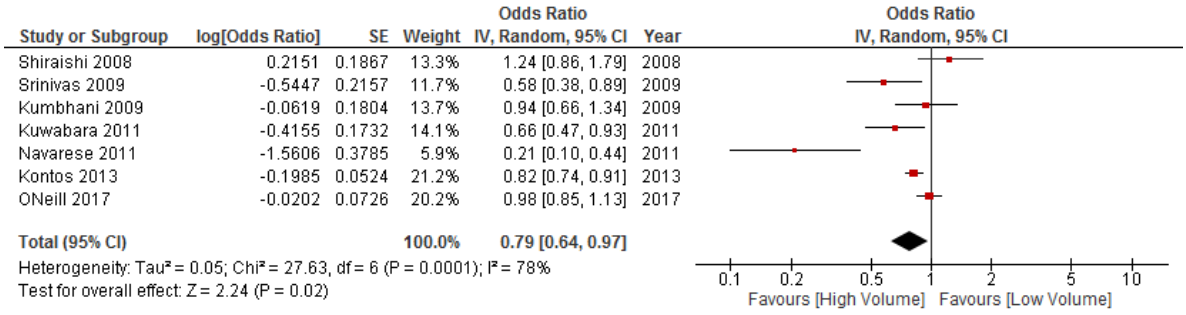


Figure A.68: Sensitivity analysis (alternative thresholds calculated for Kuwabarra et al. at < 17 and > 31 primary PCI procedures/year)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Shiraishi 2008	0.2151	0.1867	13.1%	1.24 [0.86, 1.79]	2008
Srinivas 2009	-0.5447	0.2157	11.5%	0.58 [0.38, 0.89]	2009
Kumbhani 2009	-0.2614	0.1906	12.9%	0.77 [0.53, 1.12]	2009
Kuwabara 2011	-0.2877	0.1582	14.9%	0.75 [0.55, 1.02]	2011
Navarese 2011	-1.5606	0.3785	5.7%	0.21 [0.10, 0.44]	2011
Kontos 2013	-0.1985	0.0524	21.5%	0.82 [0.74, 0.91]	2013
ONeill 2017	-0.0202	0.0726	20.5%	0.98 [0.85, 1.13]	2017
Total (95% CI)			**100.0%**	**0.78 [0.64, 0.96]**	

Heterogeneity: Tau² = 0.05; Chi² = 26.08, df = 6 (P = 0.0002); I² = 77%
Test for overall effect: Z = 2.37 (P = 0.02)

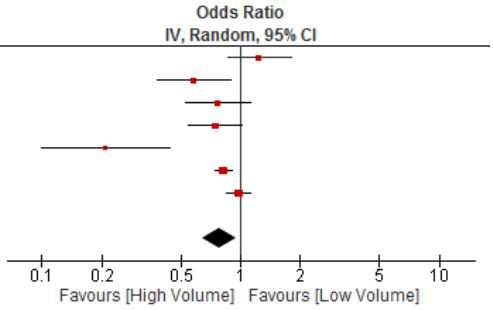


Figure A.69: Subgroup analysis: Risk of bias

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
4.1.1 Low Risk of Bias					
Srinivas 2009	-0.5447	0.2157	11.8%	0.58 [0.38, 0.89]	2009
Kontos 2013	-0.1985	0.0524	21.3%	0.82 [0.74, 0.91]	2013
ONeill 2017	-0.0202	0.0726	20.3%	0.98 [0.85, 1.13]	2017
Subtotal (95% CI)			**53.4%**	**0.84 [0.69, 1.02]**	

Heterogeneity: Tau² = 0.02; Chi² = 7.40, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 1.80 (P = 0.07)

4.1.2 Unclear Risk of Bias					
Shiraishi 2008	0.2151	0.1867	13.4%	1.24 [0.86, 1.79]	2008
Kumbhani 2009	-0.2614	0.1906	13.2%	0.77 [0.53, 1.12]	2009
Navarese 2011	-1.5606	0.3785	5.9%	0.21 [0.10, 0.44]	2011
Subtotal (95% CI)			**32.5%**	**0.63 [0.28, 1.39]**	

Heterogeneity: Tau² = 0.43; Chi² = 17.96, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 1.15 (P = 0.25)

4.1.3 High Risk of Bias					
Kuwabara 2011	-0.4155	0.1732	14.2%	0.66 [0.47, 0.93]	2011
Subtotal (95% CI)			**14.2%**	**0.66 [0.47, 0.93]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.40 (P = 0.02)

Total (95% CI)			**100.0%**	**0.77 [0.62, 0.94]**	

Heterogeneity: Tau² = 0.05; Chi² = 27.56, df = 6 (P = 0.0001); I² = 78%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Chi² = 1.72, df = 2 (P = 0.42), I² = 0%

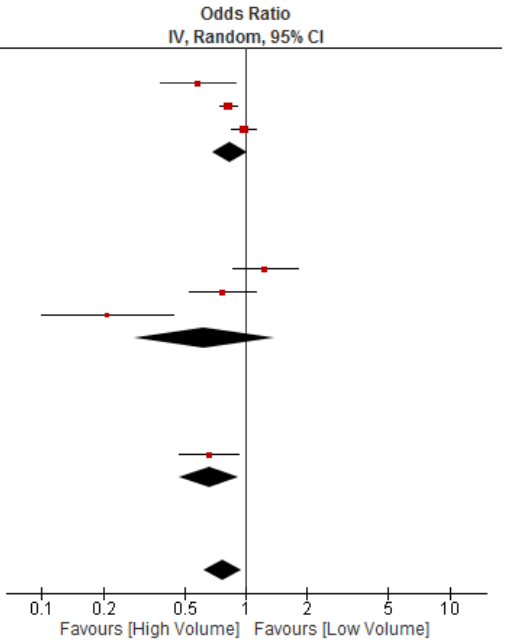


Figure A.70: Subgroup analysis: Region

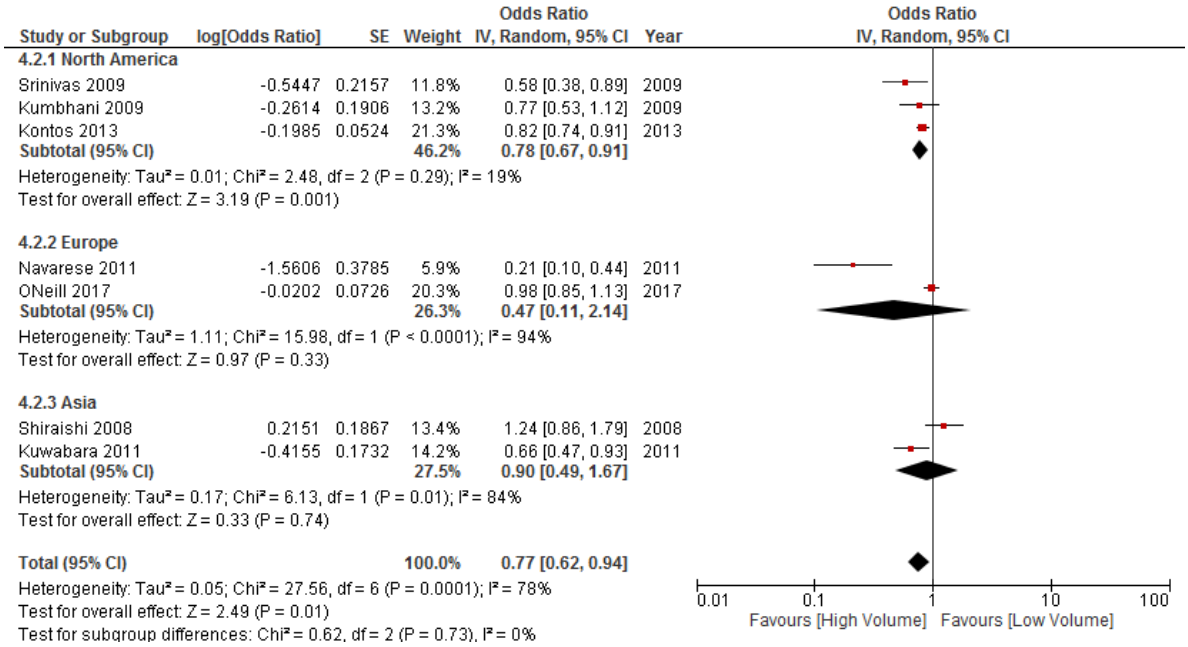


Figure A.71: Subgroup analysis: Completeness of case-mix adjustment

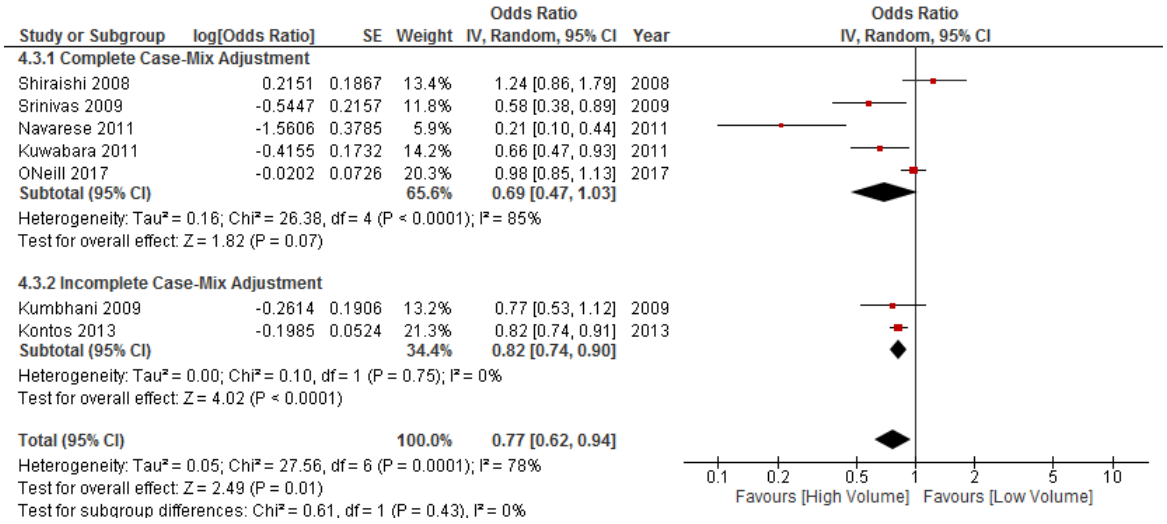


Figure A.72: Subgroup analysis: Adjusted vs. unadjusted rates

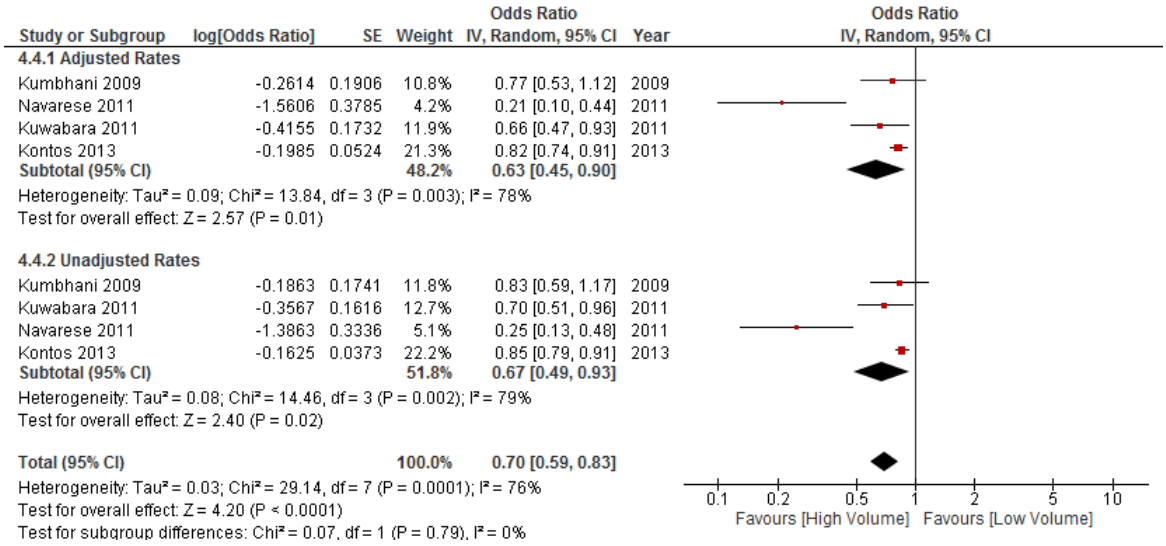


Figure A.73: Subgroup analysis: Definition of low-volume primary PCI hospital

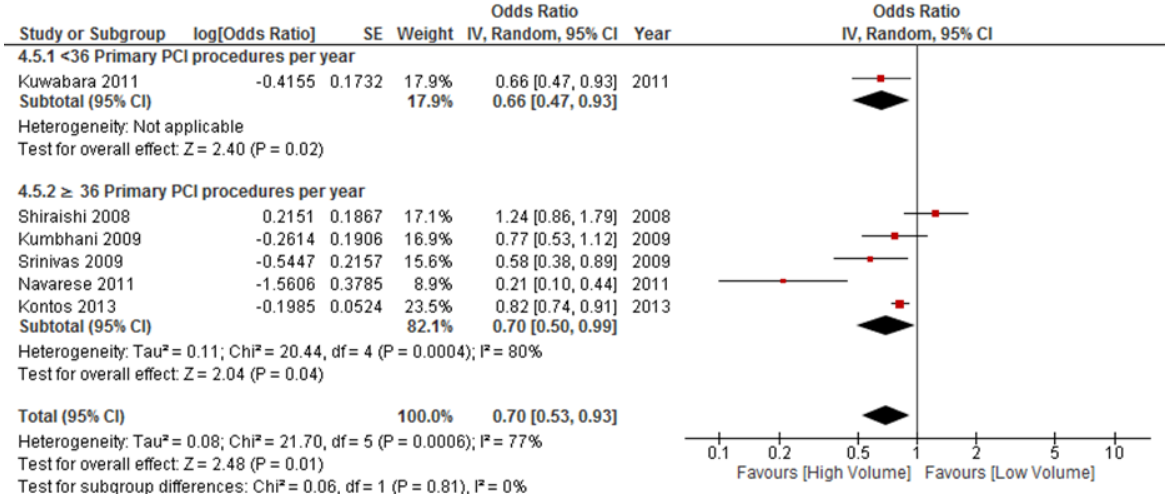


Figure A.74: Subgroup analysis: Study period

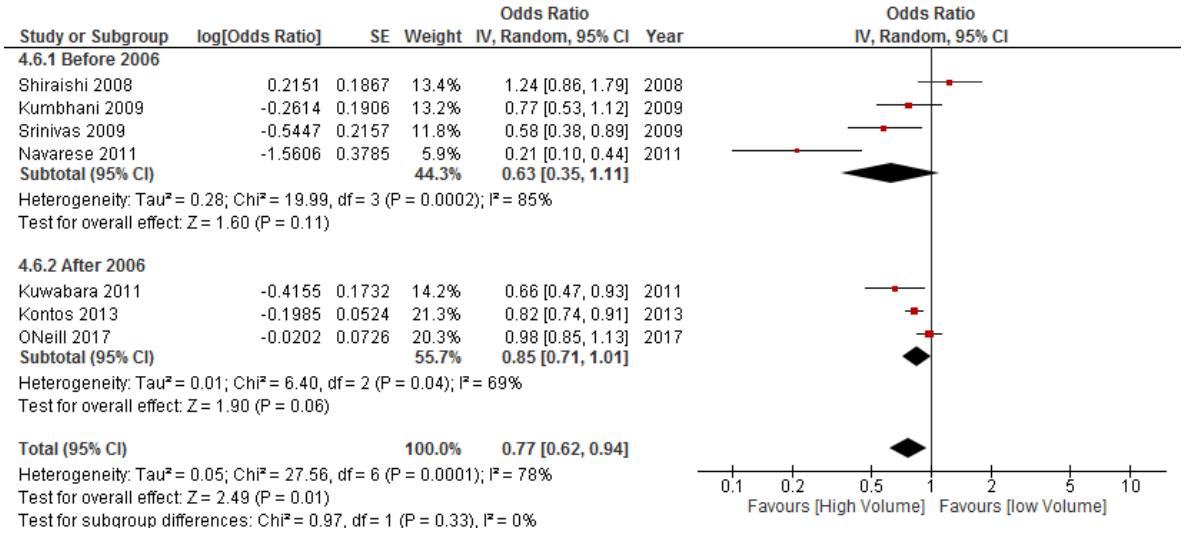
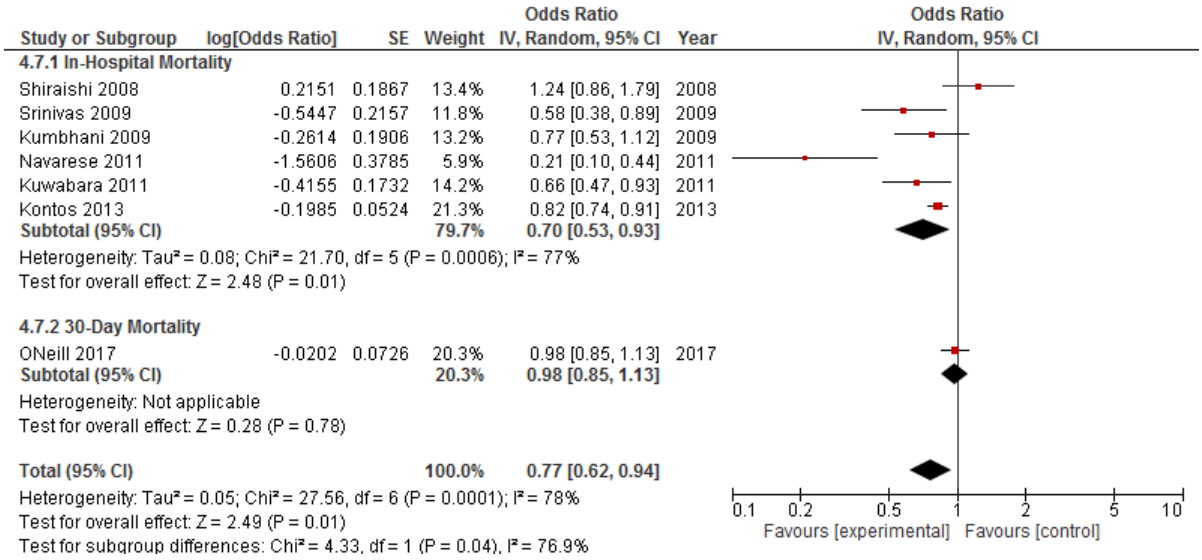


Figure A.75: Subgroup analysis examining the distribution of pooled effect sizes according to the mortality outcome used



A8.4 Sensitivity and subgroup analyses for RQ4

For all six meta-analysed outcomes in RQ4 (all-cause mortality, re-infarction, heart failure, total strokes, ischaemic stroke and major bleeding) the following sensitivity and subgroup analyses were conducted:

- Timepoint
- Fixed-effects model
- Random-effects model
- Peto odds ratio model
- Study-by-study exclusion process
- Symptom-to-needle time
- Symptom-to-balloon time
- Risk of bias
- Fibrin-specific agent
- Full-dose regimen (according to both original STREAM protocol and to the STREAM protocol as amended)
- Pre-hospital diagnosis.

With the exception of the sensitivity of the overall pooled effect estimate for total stroke outcomes highlighted in Table A.26 (which was influenced by the meta-analytical methods undertaken), the analyses indicated that all of the other pooled effect estimates were not sensitive to change and were not influenced by any particular subgroup or study. However, due to the limited number of included studies, these analyses were likely underpowered to detect an effect. Therefore for brevity, none of these forest plots are represented in this report. With regards to the meta-analysis statistical models for total stroke, the most appropriate model was selected to deal with the rarity of events, in particular the presense of single and double zero event arms (Table A.26).

Table A.26: Different meta-analysis statistical models and the impact on overall pooled effect estimate for total stroke outcome

Model	DSL Random effects (RevMan)	Fixed Effects (RevMan)	Peto Odds Ratio (RevMan)	SJ Random effects (metafor)	Independent beta-binomial (mmeta)	beta-binomial (metastan)	Beta-normal 1 (metastan)	Beta-normal 2 (metastan)
Relative Risk (95% CI)	3.39 (1.42-8.13)	3.48 (1.46-8.29)	3.19 (1.52-6.72)	3.270 (1.264-8.46)	3.947 (1.967-7.918)	1.721 (0.336-8.871)	4.256 (1.516-14.160)	4.028 (1.413-14.182)

Key: CI – confidence interval; DSL - DerSimonian-Laird; SJ - Sidik-Jonkman

Appendix 9 — GRADE summary of findings table (RQ4)

Patient or Population: Adults with ST-elevation Myocardial Infarction (STEMI)
Intervention: Pharmacoinvasive strategy
Comparison: Primary PCI
Setting: PCI-capable and non-PCI capable hospitals

Table A.27: GRADE Summary of Findings Table for RQ4

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pharmacoinvasive strategy (PI)**	**Primary PCI (pPCI)**	**Relative (95% CI)**	
RCT**:** All-cause mortality (in-hospital/30 days)										
5	randomised trials	serious [a]	not serious	not serious	serious [b]	none	57/1486 (3.8%)	58/1491 (3.9%)	**OR 0.98** (0.66 to 1.45)	⊕⊕◯◯ LOW
RCT**:** Survival (one year)										
1	randomised trials	serious [c]	N/A	not serious	N/A	none	Only one RCT reported this outcome. At 1 year, 63 patients (6.7%) had died in the PI arm, versus 56 (5.9%) in the pPCI arm (P=0.49). All-cause mortality rates tended to be numerically but not statistically significantly higher beyond the first month for the PI arm versus pPCI (log-rank P=0.495).			N/A
RCT**:** Re-infarction (in-hospital/30 days)										
5	randomised trials	serious [a]	serious [d]	not serious	serious [b]	none	28/1486 (1.9%)	28/1491 (1.9%)	**OR 0.97** (0.42 to 2.09)	⊕◯◯◯ VERY LOW
RCT**:** Heart failure (in-hospital/30 days)										
4	randomised trials	serious [e]	serious [d]	not serious	serious [b]	none	106/1309 (8.1%)	118/1313 (9.0%)	**OR 0.94** (0.64 to 1.38)	⊕◯◯◯ VERY LOW

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pharmacoinvasive strategy (PI)**	**Primary PCI (pPCI)**	**Relative (95% CI)**	
RCT**:** Cardiogenic shock (30 days)										
1	randomised trials	serious [c]	N/A	not serious	serious [f]	none	Only one RCT reported this outcome. This study found that cardiogenic shock occurred in 41/944 (4.3%) of PI group compared to 56/948 (5.9%) of pPCI group. Although there was a numerically higher event rate in the pPCI group, this was not statistically significant.			N/A
RCT**:** Cardiac mortality (30 days)										
3	randomised trials	serious [g]	not serious	not serious	serious [h]	none	Three RCTs reported this outcome. Altogether cardiac mortality occurred in 36/1292 (2.8%) in PI group and 38/1299 (2.9%) in pPCI group. All studies consistently found little to no difference between arms.			⊕⊕◯◯ LOW
RCT**:** Total stroke (in-hospital/30 days)										
4	randomised trials	serious [i]	not serious	not serious	serious [b]	none	22/1322 (1.7%)	6/1329 (0.5%)	**OR 4.26** (1.52 to 14.16)	⊕⊕◯◯ LOW
RCT**:** Ischaemic stroke (in-hospital/30 days)										
4	randomised trials	serious [i]	serious [d]	not serious	serious [b]	none	11/1456 (0.8%)	6/1461 (0.4%)	**OR 1.89** (0.56 to 6.17)	⊕◯◯◯ VERY LOW

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pharmacoinvasive strategy (PI)**	**Primary PCI (pPCI)**	**Relative (95% CI)**	
RCT**:** Intra-cranial haemorrhage (ICH) (in-hospital/30 days)										
3	randomised trials	serious [e]	not serious	not serious	serious [b]	none	Three RCTs reported this outcome, and the event only occurred in the largest of these RCTs indicating that this was a rare event. ICH occurred in 9/1292 (0.6%) in the PI group compared to 2/1299 (0.1%) in the pPCI group. In line with the event being rare, no ICH was recorded in either of the two other smaller trials. Therefore there was a numerically higher event rate in the PI group but larger studies are required to detect any statistically significant differences.			⊕⊕◯◯ LOW
RCT**:** Total bleeding (in-hospital/30 days)										
2	randomised trials	serious [j]	serious [k]	not serious	serious [h]	none	Two RCTs reported this outcome. The event occurred in 58/348 (16.7%) patients in the PI group and 28/351 (8%) of the pPCI group. In both studies any bleeding event occurred more frequently in the PI arm. However there was a moderate level of statistical heterogeneity.			⊕◯◯◯ VERY LOW
RCT**:** Major bleeding (in-hospital/30 days)										
4	randomised trials	serious [i]	not serious	not serious	serious [b]	none	67/1322 (5.1%)	48/1329 (3.6%)	**OR 1.61** (0.78 to 4.44)	⊕⊕◯◯ LOW
RCT**:** Minor bleeding (in-hospital/30 days)										
3	randomised trials	serious [e]	serious [l]	not serious	serious [b]	none	Three RCTs reported this outcome. The event occurred in 260/1292 (20.1%) patients in the PI group compared to 219/1299 (16.9%) in the pPCI group. Although two studies showed no significant difference between groups, one study showed a substantially significant difference in favour of pPCI group. There was substantial heterogeneity between studies.			⊕◯◯◯ VERY LOW

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pharmacoinvasive strategy (PI)**	**Primary PCI (pPCI)**	**Relative (95% CI)**	
RCT**:** Anaphylaxis and other adverse drug events (30 days)										
1	randomised trials	serious [c]	N/A	not serious	not serious	none	Only one RCT reported this outcome. The event occurred in 146/944 (15.5%) patients in the PI group compared to 164/948 (17.3%) patients in the pPCI group. There was no significant difference in event rate between the two groups.			N/A
Observational**:** All-cause mortality (in-hospital/30 days)										
3	observational studies	not serious	serious [d]	not serious	serious [h]	none	Three observational studies (2 at low risk of bias and 1 with unclear risk of bias) with adjusted odds ratios (and 95% Confidence Intervals) for all-cause mortality of 0.66 (0.36-1.21), 1.91 (1.01-3.50) and 2.05 (0.47-8.94) respectively. Hence two studies reported no significant association between reperfusion strategy and mortality, while one study reported a significant association between reperfusion strategy and mortality in favour of pPCI, although the statistical significance was only marginal.			⊕◯◯◯ VERY LOW
Observational**:** Total bleeding (in-hospital)										
1	observational studies	not serious	N/A	not serious	not serious	none	One study at low risk of bias reported this outcome. The adjusted Odds Ratio (and 95% confidence interval) was 0.83 (0.65-1.07). Hence no significant association was found between reperfusion strategy and total bleeding.			N/A
Observational**:** Major Bleeding (in-hospital)										

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pharmacoinvasive strategy (PI)**	**Primary PCI (pPCI)**	**Relative (95% CI)**	
2	observational studies	serious [m]	serious [n]	not serious	serious [f]	none	Two studies, one at high risk of bias and one at unclear risk of bias reported this outcome. The adjusted Odds Ratio (and 95% CI) for one study is 2.02 (0.93-4.41). However there is uncertainty around the point estimate in the other study and upon scrutiny of the absolute figures, there are concerns that the point estimates are inversed, however either way the relationship was non-significant.			⊕◯◯◯ VERY LOW

Observational**:** Survival (up to five years)

1	observational studies	not serious	N/A	not serious	N/A	none	Only one observational study reported this outcome. For all-cause mortality from the index STEMI until the end of follow-up, the pharmacoinvasive strategy was associated with improved survival in univariate (HR 0.69, 95% CI 0.52 to 0.92), but not in multivariate analysis (HR 0.84, 95% CI 0.63 to 1.12). Among 30-day survivors, the two strategies had comparable effects on all-cause mortality in both univariate and multivariate analyses. The magnitude of the effect difference between the two groups tended to be larger for early compared to late mortality, but the difference was not statistically significant.			N/A

CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio; **STEMI:** ST-elevation myocardial infarction; **PI:** Pharmacoinvasive; **PPCI:** primary percutaneous coronary intervention.

Explanations

a. Of the 6 RCTs all had an overall risk of bias with some concerns or high risk according to RoB 2 tool. However approximately half of the individual domains assessed were judged to be at low risk of bias.
b. High degree of imprecision in most studies, with the pooled effect estimate also quite broad
c. Overall high risk of bias or some concerns of bias with this study
d. Some studies showed a point estimate in favour of pharmacoinvasive strategy while others showed a point estimate in favour of primary PCI
e. Of the 4 RCTs, all had an overall risk of bias with some concerns or high risk according to RoB 2 tool. However approximately half of the individual domains assessed were judged to be at low risk of bias.
f. High degree of imprecision
g. Of the 3 RCTs all had an overall risk of bias with some concerns or high risk according to RoB 2 tool. However most of the individual domains assessed were judged to be at low risk of bias.
h. High degree of imprecision in most studies
i. Of the 5 RCTs all had an overall risk of bias with some concerns or high risk according to RoB 2 tool. However approximately half of the individual domains assessed were judged to be at low risk of bias.
j. Of the 3 RCTs all had an overall risk of bias with some concerns or high risk according to RoB 2 tool. However approximately half of the individual domains assessed were judged to be at low risk of bias.
k. I^2 of 50% indicating moderate levels of heterogeneity
l. I^2 of 79% hence substantial heterogeneity
m. Two observational studies, one with a high risk of bias and one with an unclear risk of bias
n. Uncertainty regarding the point estimate in one of the studies, which may be contributing to inconsistent findings.

Appendix 10 — Protocol deviations

During the course of the three reviews the decision was taken to make minor deviations to the protocol to ether improve the methodology or for reasons of practicality.

The following is a list of protocol deviations:

The order of presentation of the reviews was changed from the original protocol as when read in full it made more sense to present protocol RQ3: "What international models for specialist cardiac networks exist that might be applicable to the Irish healthcare system" first, followed by protocol RQ1: "What standards do interational guidelines recommend for centres performing PCI?" and finally protocol RQ2: "What standards do international guidelines recommend for centres providing PCI".

RQ1:

- Studies published before 2008 were included if referenced in an included publication and had information on a network that was considered pertinent.
- Studies with inadequate information on a network, such as conference abstracts that were not published in full, were excluded.
- Reviews, editorials and commentaries were excluded.
- Data extraction was performed by one reviewer, double checked by another reviewer and where necessary, a third reviewer.

RQ2:

- For clarity the title was reworded to: "Organisational and service specification recommendations for centres providing percutaneous coronary interventions".
- In addition to the protocol search strategy, other search methods used included scanning the reference list of included studies and the reference lists of studies (such as editorials and guideline reviews) captured by the initial search, which were highlighted as potentially referencing eligible guidance documents during title and abstract screening.
- The exclusion criteria were expanded to include guidelines, standards and recommendations that adopted other guidance documents in full.
- It was also decided that those guidance documents that only had recommendations in relation to time-to treatment criteria or that focused on specific sub-populations(e.g. LMPCI, CTO, congenital heart disease) or that

focussed on specific techniques (e.g. trans-radial access, thrombectomy) would be excluded from the main review but would be collated and presented in the appendix.

- The AGREE II tool was used to evaluate all guidance documents, not just guidelines, to allow for comparison between guidance documents.

RQ3:

- Where studies reported analyses based on multiple plausible thresholds, the model using a threshold most similar to other included studies was selected.
- In terms of sensitivity and subgroup analyses, as no study defined a low volume hospital for primary PCI as 100 procedures per year, a decision was made to change this threshold to 36 primary PCI per year in line with American guideline recommendations.
- Due to the combination of in-hospital and 30-day mortality outcomes used, a post-hoc sub group analysis was performed to assess the differences in findings between those that reported in-hospital and those that reported 30-day mortality.
- For one meta-analysis where a temporal trend was observed, a random-effects cumulative meta-analysis was conducted using STATA version 13 (StataCorp, College Station, TX, USA) using the median year of study data.
- Random-effects meta-regression was conducted (as opposed to fixed-effects meta-regression) as it was deemed more appropriate given that it was not possible to assume that all the heterogeneity could be explained by the covariates as is required for fixed-effects meta-regression.
- As there were fewer than ten studies in each meta-analysis, the meta-regression analysis was exploratory in nature.
- Meta-regression was conducted using the following additional covariates; mean volume in lowest and highest groups; regions and total number of groupings.
- Publication bias was not formally assessed as the minimum requirement of 10 studies was not met in any single meta-analysis in order to conduct this test; however funnels plots were visually inspected.
- The certainty of the evidence for each outcome was assessed using the GRADE approach.

RQ4:

- Studies were excluded if coronary angiography took place greater than 24 hours post fibrinolytic administration, unless the protocol explicitly aimed for <24 hours but this could not occur in a proportion of patients due to system delays.
- Due to the rarity of certain outcomes, Bayesian meta-analyses using beta-normal hierarchical models were undertaken in statistical software R using MetaStan programme for these outcomes with zero event arms.
- The number needed to treat for one additional harmful outcome (NNTH) was only estimated for outcomes that were found to be statistically significant.
- The following sensitivity and subgroup analyses were conducted on meta-analyses of RCTs and not observational studies due to the limited number of included studies per outcome for the latter:
    - random effects model, by timepoint and then in-hospital/30-day combined
    - fixed effects
    - peto odds ratio
    - study-by-study exclusion process
    - study period – no study period older than 2006, hence not conducted
    - symptom-to-needle time: ≤ 2 hours vs. > 2 hours
    - symptom-to-balloon time: ≤ 3 hours vs. > 3 hours
    - risk of bias (RoB) based on randomisation process domain[1]: Low RoB, vs. Some concerns vs. High RoB
    - fibrin-specific vs. non-fibrin-specific vs. mixture
    - full-dose regimen[2] vs. non-full-dose regimen
    - STEMI diagnosis pre PCI-capable hospital vs. STEMI diagnosis in PCI-capable hospital.

[1]RoB based on randomisation process domain as overall RoB domain believed to be unduly strict.[2] Full-dose regimen analysis conducted twice to account for a mid-study protocol change for the STREAM study reducing the fibrinolytic dose in older patients.

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