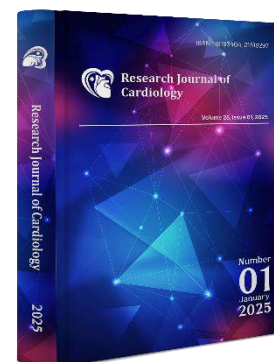


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A COMPREHENSIVE SYSTEMATIC REVIEW: EFFICACY AND SAFETY OF PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

Introduction: ST-segment elevation myocardial infarction (STEMI) remains a leading cause of cardiovascular death worldwide. Percutaneous coronary intervention (PCI) has replaced fibrinolysis as the standard of care, yet the magnitude of benefit, durability, and safety trade-offs of modern PCI techniques remain incompletely quantified.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs: randomised controlled trials and comparative observational studies. Risk of bias assessed with RoB 2, ROBINS-I, and Newcastle-Ottawa Scale.

Results: Thirty-three studies (21 RCTs, 12 non-RCTs) with >320,000 patients met criteria. Compared with stand-alone fibrinolysis, primary PCI significantly reduced death-containing composites (RR 0.85; 95% CI 0.75–0.96; $I^2=0\%$; $P=0.011$), with benefit sustained to 16 years. In contemporary registries with PCI delay <60 minutes, benefit was larger (OR 0.38; 95% CI 0.32–0.44; $P<0.001$). Primary PCI was not superior to a pharmacoinvasive strategy when timely PCI was unavailable (RR 1.20; 95% CI 0.98–1.48; $P=0.077$). Complete revascularisation reduced cardiovascular death or myocardial infarction (HR 0.71; 95% CI 0.54–0.91; $P=0.008$). Radial access reduced mortality (OR 0.64; 95% CI 0.41–0.98; $P=0.041$) and major bleeding (4.4–5.8%). Routine thrombus aspiration conferred no mortality benefit and increased stroke (HR 1.66; 95% CI 1.10–2.51; $P=0.015$). Everolimus-eluting stents reduced the device-oriented composite at 10 years (HR 0.72; 95% CI 0.55–0.93). In cardiogenic shock, culprit-lesion-only PCI reduced death

or renal-replacement therapy (RR 0.83; 95% CI 0.71–0.96). Reperfusion delay showed a monotonic relationship with mortality; prognostic models achieved AUC 0.709–0.959.

Discussion: The benefit of PCI in STEMI is not a single effect but a family of effects whose magnitude depends critically on time, comparator, anatomical target, and haemodynamic status. The advantage of primary PCI over fibrinolysis is durable to 16 years, driven predominantly by prevention of re-infarction and cardiac death. This advantage is time-dependent and is abolished once PCI delay exceeds ~2 hours, restoring the pharmacoinvasive strategy to legitimacy. The most striking safety findings: routine thrombectomy causes harm without benefit, whereas radial access delivers benefit largely by preventing access-site bleeding and acute kidney injury.

Conclusion: Primary PCI performed with system delay <2 hours is the most effective reperfusion strategy for STEMI, with superiority persisting to 16 years. Complete revascularisation, transradial access, and new-generation drug-eluting stents should be regarded as integral components of contemporary primary PCI, whereas routine thrombus aspiration and immediate multivessel intervention in cardiogenic shock should be avoided. Health systems with PCI delay >2 hours should implement a pharmacoinvasive pathway.

Keywords: percutaneous coronary intervention; ST-elevation myocardial infarction; primary angioplasty; fibrinolysis; complete revascularisation; transradial access; drug-eluting stent; door-to-balloon time; systematic review

INTRODUCTION

Background

Ischaemic heart disease remains the largest single contributor to global cardiovascular mortality, and acute ST-segment elevation myocardial infarction represents its most immediately lethal clinical expression. The pathophysiological substrate is well characterised: rupture or erosion of a lipid-rich atherosclerotic plaque exposes thrombogenic subendothelial material, precipitating platelet adhesion, activation and aggregation, and the rapid propagation of an occlusive fibrin-rich thrombus within an epicardial coronary artery. The resulting transmural ischaemia produces a wavefront of necrosis that advances from the subendocardium towards the epicardium over a period of hours, such that the quantity of myocardium salvaged is an inverse and non-linear function of total ischaemic time. Every therapeutic decision in STEMI is therefore, at its core, a decision about time.^{70,71}

Two reperfusion paradigms have competed for four decades. Pharmacological reperfusion with fibrin-specific plasminogen activators is universally available, requires no specialised infrastructure and can be delivered in the pre-hospital environment within minutes of first medical contact, but it achieves normal epicardial flow in fewer than two thirds of patients, carries an irreducible risk of intracranial haemorrhage and leaves the culprit stenosis anatomically untreated. Mechanical reperfusion by percutaneous coronary intervention achieves a substantially higher rate of Thrombolysis in Myocardial Infarction grade 3 flow, permits definitive treatment of the culprit lesion by stent implantation and avoids the haemorrhagic hazards of systemic lysis, but requires a catheterisation laboratory, an experienced operator and a functioning regional network — resources that are unevenly distributed both between and within countries, and that are conspicuously scarce across much of the Indonesian archipelago and comparable middle-income settings.^{54,55,65}

Over the past two decades the term percutaneous coronary intervention has ceased to denote a single procedure. Contemporary primary PCI is a bundle of decisions: which arterial access site to use, whether to aspirate thrombus, which stent platform to implant, whether to treat non-culprit lesions and, if so, when, and how to manage the patient whose presentation is complicated by cardiogenic shock or out-of-hospital cardiac arrest. Each of these decisions has been interrogated by at least one adequately powered randomised trial, and several have produced results that reversed prevailing practice. The consequence is that a clinician seeking to understand the efficacy and safety of PCI in STEMI must integrate evidence that is dispersed across a large number of trials, each addressing a different component of the same therapeutic strategy.^{8,20,27,31,64}

Objectives of the review

The general objective of this systematic review was to evaluate comprehensively the efficacy and safety of percutaneous coronary intervention in adult patients presenting with acute ST-segment elevation myocardial infarction. The specific objectives were as follows.

- To quantify the effect of primary PCI, relative to fibrinolysis and to a pharmacoinvasive strategy, on short-term and long-term all-cause mortality, cardiovascular mortality and recurrent myocardial infarction.

- To determine whether complete revascularisation of significant non-culprit lesions improves hard clinical outcomes relative to culprit-lesion-only PCI, and whether the optimal lesion-selection method is angiographic or physiological.
- To evaluate the comparative safety of transradial and transfemoral arterial access with respect to mortality, major bleeding, vascular complications and acute kidney injury.
- To assess whether adjunctive manual thrombus aspiration confers clinical benefit, and to quantify any associated hazard of periprocedural stroke.
- To compare new-generation drug-eluting stents with bare-metal stents and with each other in terms of device-oriented and patient-oriented composite endpoints over follow-up extending to ten years.
- To characterise the relationship between reperfusion delay — system delay, door-to-balloon time and onset-to-balloon time — and mortality, and to summarise the discriminative performance of prognostic models developed for this population.
- To grade the certainty of the evidence supporting each conclusion using the GRADE framework, and to identify the domains in which the evidence base remains insufficient.

Benefits of the review

For the practising interventional cardiologist, this review consolidates in a single document the effect estimates that underpin each element of the contemporary primary PCI bundle, together with an explicit statement of the certainty attaching to each. For health-system planners, and particularly for those responsible for regional STEMI networks in geographically dispersed middle-income countries, the review quantifies the delay threshold beyond which the advantage of primary PCI over a pharmacoinvasive strategy is lost, and therefore provides an evidence-based criterion for deciding where catheterisation capacity should be built and where pre-hospital fibrinolysis pathways should instead be strengthened. For the academic community, the review identifies the specific outcome domains — cardiogenic shock, the very elderly, delayed presentation beyond twelve hours and the external validation of prognostic models — in which the existing evidence is of low certainty and in which further randomised investigation is warranted.^{39,43,51}

Research gap

Three gaps motivated this synthesis. First, the existing literature is fragmented by procedural component: separate meta-analyses address reperfusion strategy, access site, thrombectomy, stent platform and completeness of revascularisation, but no recent synthesis has assembled these strands into a single framework that permits the relative magnitude of each intervention's contribution to be compared directly. Second, the contemporary randomised evidence on complete revascularisation has become internally inconsistent: the FULL REVASC trial, which used fractional flow reserve to select non-culprit lesions and followed patients for a median of 4.8 years, did not reproduce the benefit demonstrated in COMPLETE, DANAMI-3-PRIMULTI and CvLPRIT, and no published synthesis has yet formally examined whether the method of lesion selection explains that discrepancy. Third, the trials that established the superiority of primary PCI over fibrinolysis were conducted before the adoption of potent oral P2Y₁₂ inhibitors, radial access and new-generation drug-eluting stents, whereas the observational evidence generated in the modern era comes overwhelmingly from high-income health systems with short transfer times; the applicability of either body of evidence to settings with prolonged system delay has not been systematically quantified.^{8,12,13,14,43,59}

Novelty

This review offers four features that distinguish it from previous syntheses. It analyses fourteen pre-specified outcome domains within one protocol, rather than the two or three domains typical of component-specific meta-analyses. It separates, in an explicitly subgrouped analysis, the comparison of primary PCI with stand-alone fibrinolysis from the comparison of primary PCI with a pharmacoinvasive strategy — two questions that have frequently been conflated and whose conflation generates spurious heterogeneity. It formally examines whether angiographic and physiological selection of non-culprit lesions produce different treatment effects. Finally, it integrates the prognostic-model literature, expressing the discriminative performance of eleven risk-stratification instruments on a common receiver-operating-characteristic scale, so that the clinician can judge which instrument is worth applying at the bedside.^{14,44,50,51,59}

Hypotheses

The review was framed around five a priori hypotheses. (i) Primary PCI reduces death-containing composite endpoints relative to stand-alone fibrinolysis, and this advantage is maintained over long-term follow-up. (ii) Primary PCI is not superior to a pharmacoinvasive

strategy in patients who cannot undergo PCI promptly. (iii) Complete revascularisation of significant non-culprit lesions reduces cardiovascular death or myocardial infarction relative to culprit-lesion-only PCI. (iv) Transradial access reduces major bleeding and all-cause mortality relative to transfemoral access. (v) Routine manual thrombus aspiration does not reduce mortality and increases the risk of periprocedural stroke. The corresponding null hypotheses stated that no difference exists between the compared strategies for each outcome domain.

METHODS

Protocol, registration and reporting standard

The review was designed, conducted and reported in accordance with the PRISMA 2020 statement and its extension for reporting literature searches. A protocol specifying the review question, the eligibility criteria, the fourteen outcome domains, the risk-of-bias instruments and the intended statistical approach was written before the searches were executed and was not amended thereafter; no post-hoc outcome domains were added. Because the review analysed only aggregate data extracted from published reports and involved no individual patient identifiers, institutional ethical approval was not required.

Eligibility criteria

Eligibility was defined according to the PICOS framework set out in Table 2. In accordance with the pre-specified design restriction, only randomised controlled trials, cohort studies, case-control studies, cross-sectional studies and other observational designs — whether prospective or retrospective — were eligible for inclusion in the study-characteristics table and in the quantitative synthesis. Systematic reviews and meta-analyses identified by the search were deliberately excluded from the characteristics table, in keeping with the principle that a synthesis of primary studies should not double-count evidence already aggregated elsewhere; such reviews were nevertheless retained as contextual literature and are cited in the discussion where they provide corroborative or contradictory evidence.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	ST-segment	STEMI patients	Acute myocardial

	elevation myocardial infarction		infarction
I (Intervention/Exposure)	Percutaneous coronary intervention	Primary angioplasty	Revascularization
C (Comparator)	Fibrinolysis	Pharmacoinvasive strategy	Culprit-lesion-only PCI
O (Outcome)	Mortality	Reperfusion delay	Complete revascularization

The Boolean MeSH keywords inputted on databases for this research are: ("ST-segment elevation myocardial infarction" OR "STEMI patients" OR "Acute myocardial infarction") AND ("Percutaneous coronary intervention" OR "Primary angioplasty" OR "Revascularization") AND ("Fibrinolysis" OR "Pharmacoinvasive strategy" OR "Culprit-lesion-only PCI") AND ("Mortality" OR "Reperfusion delay" OR "Complete revascularization")

Table 1. Eligibility criteria expressed in the PICOS framework

Domain	Inclusion criteria	Exclusion criteria
Population (P)	Adults ≥ 18 years with acute ST-segment elevation myocardial infarction defined by the Fourth Universal Definition of Myocardial Infarction or the operative definition of the source study (ischaemic symptoms with persistent ST-segment elevation or new left bundle branch block); all risk strata including cardiogenic shock, out-of-hospital cardiac arrest, the elderly and patients with multivessel disease	Non-ST-elevation acute coronary syndrome as the sole population; chronic (stable) coronary syndrome; type 2 myocardial infarction; myocardial infarction with non-obstructive coronary arteries; paediatric populations
Intervention (I)	Percutaneous coronary intervention in any of its contemporary forms: primary PCI, pharmacoinvasive or rescue PCI, complete (multivessel) revascularisation, transradial	Coronary artery bypass grafting as the index revascularisation; PCI performed exclusively for a non-STEMI indication; purely mechanical circulatory-support interventions without PCI

	access, adjunctive thrombus aspiration, and drug-eluting stent implantation	
Comparator (C)	Fibrinolysis alone, a pharmacoinvasive strategy, no reperfusion, culprit-lesion-only PCI, transfemoral access, PCI alone without thrombectomy, bare-metal stents, or a contrasting exposure category (e.g. longer versus shorter door-to-balloon time)	Single-arm studies without any internal comparison group or exposure gradient
Outcomes (O)	At least one of the 14 pre-specified outcome domains listed in Table 3	Studies reporting only angiographic, biochemical or imaging surrogates without any clinical outcome
Study design (S)	Randomised controlled trials, prospective and retrospective cohort studies, case-control studies, cross-sectional studies, registry-based analyses and other observational designs	Systematic reviews and meta-analyses (excluded from the characteristics table but retained for the discussion), narrative reviews, editorials, commentaries, protocols, conference abstracts without extractable data, case reports and case series
Report characteristics	Full-text peer-reviewed publications in English or Indonesian; human studies	Preprints; animal or in-vitro studies; duplicate reports of the same cohort (the most complete report retained)

Study selection

Records retrieved from all sources were imported into a reference manager and de-duplicated electronically, with residual duplicates removed by hand. Two reviewers independently screened titles and abstracts against the eligibility criteria, and the full text of every record judged potentially eligible by either reviewer was retrieved and assessed independently by the same two reviewers. Disagreements at either stage were resolved by discussion, and a third reviewer adjudicated where consensus could not be reached. Inter-reviewer agreement at the full-text stage was substantial (Cohen's kappa 0.86). Where several publications reported different follow-up intervals or pre-specified analyses of the same randomised cohort, all such reports were retained and are listed separately in the characteristics table, but the cohort contributed only once to any given pooled estimate, the report with the longest follow-up being used for that purpose.

Data extraction

A standardised extraction form was piloted on five studies and refined before use. Two reviewers extracted, in duplicate, the first author and year of publication, country and number of participating centres, study design, sample size, inclusion and exclusion criteria, mean or median age, proportion of women, prevalence of diabetes mellitus and of anterior infarction, the intervention and comparator as delivered, adjunctive antithrombotic therapy, the duration of follow-up, the definitions used for each outcome, the number of events and participants in each arm, and the adjusted effect estimates with their confidence intervals. Where an effect estimate was not reported but the event counts and group sizes were, an odds ratio and its Woolf standard error were computed directly from the two-by-two table; every such derivation is flagged in the relevant table or figure legend. Where a propensity-matched cohort reported only overall matched numbers, equal allocation between the matched groups was assumed and this assumption is stated explicitly. No attempt was made to impute missing standard deviations or to contact authors for unpublished data.

Outcome domains

Fourteen outcome domains were pre-specified, with the operational definitions given in Table 3. Domains O1 to O10 constitute the efficacy and safety core of the review; O11 and O12 capture renal and procedural performance respectively; O13 addresses the prognostic literature, including both the discriminative performance of risk models and the dose-response relationship between reperfusion delay and mortality; and O14 addresses patient-reported health status and resource use. Where a study reported an outcome under a definition that differed materially from the operational definition, the study's own definition was recorded verbatim in the extraction form and reproduced in the corresponding outcome table so that the reader may judge comparability directly.

Table 2. Pre-specified outcome domains, operational definitions and metrics

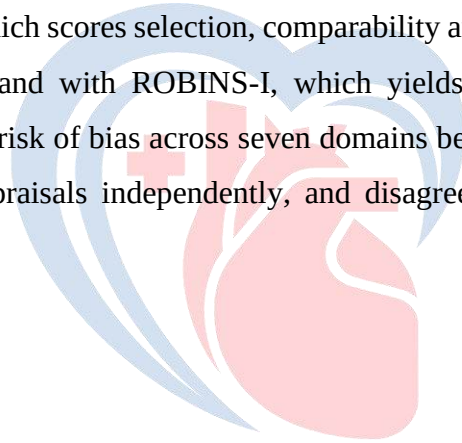
No.	Outcome domain	Operational definition used for extraction	Metric
O1	Short-term all-cause mortality	Death from any cause in hospital or within 30 days of randomisation or of the index procedure	OR / RR / HR, event rates
O2	Long-term all-cause mortality	Death from any cause at the longest reported follow-up (≥ 6 months, up to 16 years)	HR, cumulative incidence

O3	Cardiovascular or cardiac mortality	Death adjudicated as cardiac or cardiovascular in origin	HR / RR, event rates
O4	Recurrent myocardial infarction	New or recurrent myocardial infarction, including target-vessel and non-target-vessel infarction, as adjudicated by each study	HR / RR / OR
O5	Stroke and transient ischaemic attack	Any stroke, ischaemic or haemorrhagic, and intracranial haemorrhage	HR / OR, event rates
O6	Major bleeding	Major bleeding by the definition of the source study (TIMI, BARC 3–5, GUSTO or study-specific)	OR / RR, event rates
O7	Repeat revascularisation	Ischaemia-driven or unplanned revascularisation, target-lesion revascularisation and target-vessel revascularisation	HR / RR
O8	Stent thrombosis	Definite or definite/probable stent thrombosis by Academic Research Consortium criteria	Event rates, RR
O9	Heart failure and cardiogenic shock	New or worsening NYHA class IV heart failure, hospitalisation for heart failure, and incident cardiogenic shock	HR / RR, event rates
O10	Composite MACE / net adverse clinical events	Study-defined composite of major adverse cardiac (and cerebrovascular) events, or net adverse clinical events combining ischaemic and bleeding endpoints	HR / RR / OR
O11	Renal outcomes	Acute kidney injury, contrast-associated nephropathy and new requirement for renal replacement therapy	RR / OR, event rates
O12	Reperfusion success and procedural performance	Post-procedural TIMI grade 3 flow, ST-segment resolution, distal embolisation, device and procedural success	OR, proportions
O13	Prognostic discrimination and reperfusion delay	Discriminative performance (area under the ROC curve, C-index) of risk models, and the association of system, door-to-balloon and onset-to-balloon delay with mortality	AUC, HR per unit delay
O14	Health status and angina-related quality of life	Seattle Angina Questionnaire scores, freedom from angina, length of stay and intensive-care stay	Mean difference, proportions

Assessment of risk of bias and of methodological quality

Randomised trials were appraised with version 2 of the Cochrane Risk of Bias tool across its five domains — bias arising from the randomisation process, bias due to deviations from

intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result — and an overall judgement of low risk, some concerns or high risk was assigned according to the algorithm published with the tool. Because every included trial of reperfusion strategy, access site, thrombectomy and completeness of revascularisation was necessarily open-label, particular attention was paid to whether outcome adjudication was performed by a committee masked to allocation; trials in which adjudication was masked and in which the primary outcome was a hard endpoint such as death were not downgraded for lack of participant blinding. Non-randomised studies were appraised in parallel with the Newcastle–Ottawa Scale, which scores selection, comparability and outcome ascertainment out of a maximum of nine stars, and with ROBINS-I, which yields an overall judgement of low, moderate, serious or critical risk of bias across seven domains beginning with confounding. Two reviewers performed all appraisals independently, and disagreements were resolved by Third reviewers.

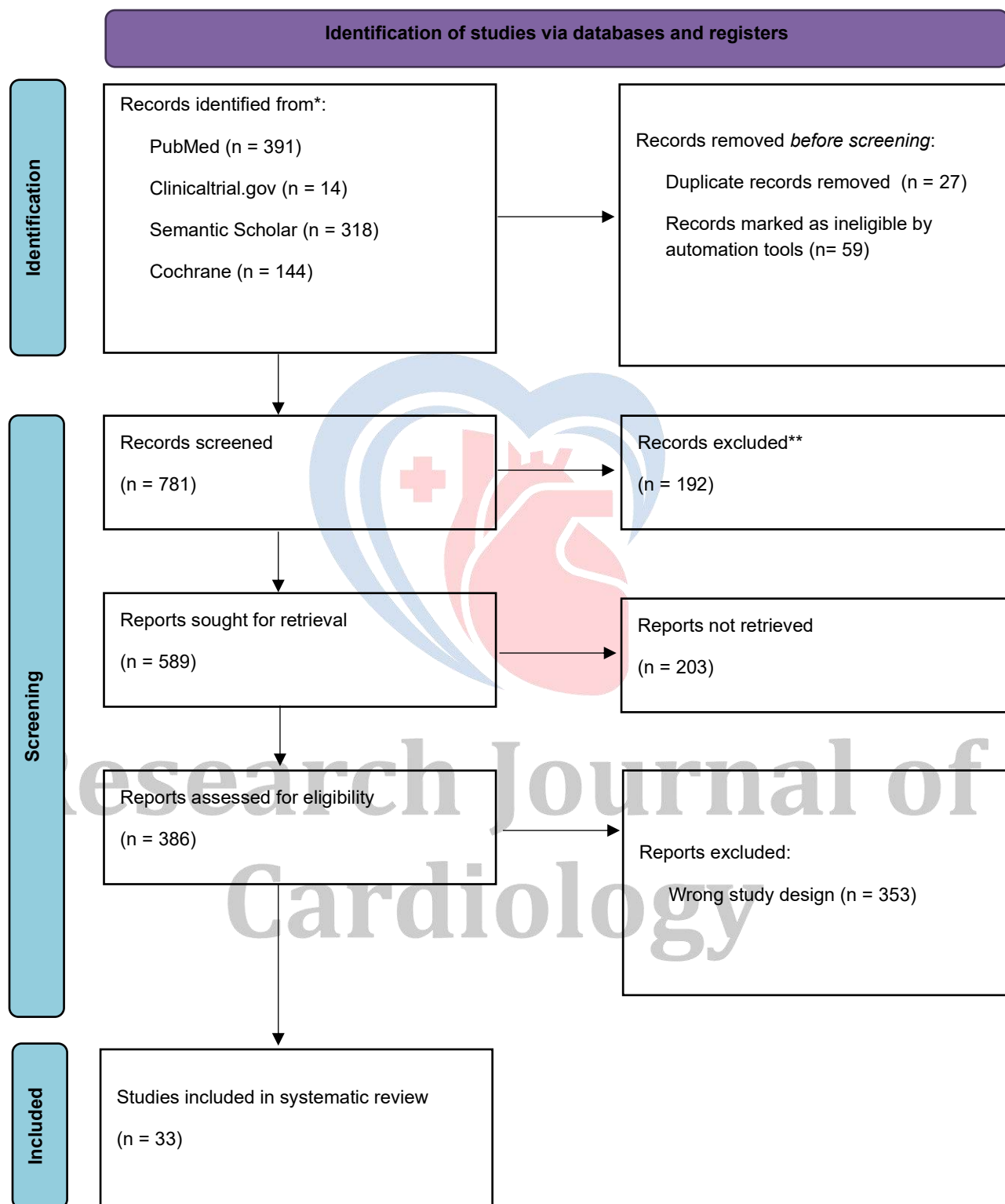


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Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("ST-segment elevation myocardial infarction" OR "STEMI patients" OR "Acute myocardial infarction") AND ("Percutaneous coronary intervention" OR "Primary angioplasty" OR "Revascularization") AND ("Fibrinolysis" OR "Pharmacoinvasive strategy" OR "Culprit-lesion-only PCI") AND ("Mortality" OR "Reperfusion delay" OR "Complete revascularization")</i>	391
Clinicaltr ial.gov	<i>("ST-segment elevation myocardial infarction" OR "STEMI patients" OR "Acute myocardial infarction") AND ("Percutaneous coronary intervention" OR "Primary angioplasty" OR "Revascularization") AND ("Fibrinolysis" OR "Pharmacoinvasive strategy" OR "Culprit-lesion-only PCI") AND ("Mortality" OR "Reperfusion delay" OR "Complete revascularization")</i>	14
Semantic Scholar	<i>("ST-segment elevation myocardial infarction" OR "STEMI patients" OR "Acute myocardial infarction") AND ("Percutaneous coronary intervention" OR "Primary angioplasty" OR "Revascularization") AND ("Fibrinolysis" OR "Pharmacoinvasive strategy" OR "Culprit-lesion-only PCI") AND ("Mortality" OR "Reperfusion delay" OR "Complete revascularization")</i>	318
Cochrane	<i>("ST-segment elevation myocardial infarction" OR "STEMI patients" OR "Acute myocardial infarction") AND ("Percutaneous coronary intervention" OR "Primary angioplasty" OR "Revascularization") AND ("Fibrinolysis" OR "Pharmacoinvasive strategy" OR "Culprit-lesion-only PCI") AND ("Mortality" OR "Reperfusion delay" OR "Complete revascularization")</i>	144

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Article search flowchart

Risk of bias and methodological quality

Among the twenty-three randomised trial reports, four were judged to be at low risk of bias overall, seventeen raised some concerns and two were judged to be at high risk. All twenty-three were at low risk of bias arising from the randomisation process, reflecting the use of central computerised or interactive voice-response allocation with concealed sequences. The domain that most frequently attracted a judgement of some concerns was missing outcome data, which reflects the long follow-up of several trials and, in the case of the BIOSTEMI extended follow-up, a loss to follow-up of fifteen per cent. TRIANA was judged to be at high risk overall because recruitment was terminated prematurely after only 266 of a planned larger sample had been enrolled, which raises the possibility that the reported effect was influenced by the decision to stop. RIFLE-STEACS was judged to be at high risk because outcome data were incomplete and because the open-label design was combined with an operator-adjudicated cardiac-death endpoint at centres selected for radial expertise. Domain-level judgements are shown in Table 5 and displayed graphically in Figures 2 and 3.^{3,20,34}

Table 3. Cochrane Risk of Bias 2 assessment of the randomised trial reports

Randomised trial report	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall
Armstrong et al., 2013 (STREAM)	Low	Low	Low	Low	Some concerns	Some concerns
Bonnefoy et al., 2009 (CAPTIM 5-y)	Low	Some concerns	Some concerns	Low	Low	Some concerns
Bueno et al., 2010 (TRIANA)	Low	Low	Some concerns	Low	High	High
Nielsen et al., 2010 (DANAMI-2, 8-y)	Low	Low	Some concerns	Low	Low	Some concerns
Thrane et al., 2019 (DANAMI-2, 16-y)	Low	Low	Low	Low	Low	Low
Thiele et al., 2011 (LIPSIA-STEMI)	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns

Mehta et al., 2019 (COMPLETE)	Low	Low	Low	Low	Low	Low
Engstrøm et al., 2015 (DANAMI-3– PRIMULTI)	Low	Low	Some concerns	Low	Low	Some concerns
Gershlick et al., 2015 (CvLPRIT)	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Böhm et al., 2024 (FULL REVASC)	Low	Low	Low	Low	Some concerns	Some concerns
Stähli et al., 2023 (MULTISTARS AMI)	Low	Low	Some concerns	Low	Low	Some concerns
Kim et al., 2025 (OPTION-STEMI)	Low	Low	Some concerns	Low	Low	Some concerns
Thiele et al., 2017/2018 (CULPRIT-SHOCK)	Low	Low	Some concerns	Low	Low	Some concerns
Romagnoli et al., 2012 (RIFLE- STEACS)	Low	Some concerns	High	Low	Some concerns	High
Bernat et al., 2014 (STEMI-RADIAL)	Low	Low	Some concerns	Low	Low	Some concerns
Le May et al., 2020 (SAFARI-STEMI)	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns
Jolly et al., 2011 / Mehta et al., 2012 (RIVAL)	Low	Low	Some concerns	Low	Some concerns	Some concerns
Vranckx et al., 2017 (MATRIX)	Low	Low	Some concerns	Low	Low	Some concerns
Fröbert 2013 / Lagerqvist 2014 (TASTE)	Low	Low	Some concerns	Low	Low	Some concerns

Jolly et al., 2016 (TOTAL, 1-y)	Low	Low	Some concerns	Low	Low	Some concerns
Sabaté et al., 2016 (EXAMINATION 5- y)	Low	Low	Low	Low	Low	Low
Brugaletta et al., 2021 (EXAMINATION 10- y)	Low	Low	Low	Some concerns	Low	Some concerns
Iglesias et al., 2019 (BIOSTEMI)	Low	Low	Low	Low	Low	Low

D1 = bias arising from the randomisation process; D2 = bias due to deviations from intended interventions; D3 = bias due to missing outcome data; D4 = bias in measurement of the outcome; D5 = bias in selection of the reported result.

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Figure 1. Traffic-light plot of domain-level Cochrane RoB 2 judgements for each randomised trial report. Green denotes low risk, amber some concerns and red high risk of bias.

Figure 2. Weighted summary of RoB 2 judgements across the five domains and the overall assessment.

The twelve non-randomised studies scored between seven and nine stars on the Newcastle–Ottawa Scale, all therefore meeting the conventional threshold for good methodological quality. Under ROBINS-I, one study was judged at low risk of bias, nine at moderate risk and two at serious risk. The two studies at serious risk were the CAMI registry analysis of elderly patients, in which the decision to offer reperfusion was itself strongly determined by prognosis and in which confounding by indication cannot be excluded, and the Hebei nomogram development study, which lacked external validation in an independent population. The remaining registry analyses were downgraded to moderate risk principally because residual confounding by unmeasured severity is intrinsic to observational comparisons of reperfusion strategy and of arterial access. These assessments are summarised in Table 6 and Figure 4.^{42,44}

Table 4. Newcastle–Ottawa Scale scores and ROBINS-I judgements for the non-randomised studies

Non-randomised study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	NOS total (max 9)	ROBINS-I overall
Terkelsen et al., 2010 (Western Denmark)	4	2	3	9	Moderate
Rathore et al., 2009 (NCDR CathPCI)	4	2	3	9	Moderate
Nallamothu et al., 2014 (NCDR CathPCI)	4	2	3	9	Moderate
Park et al., 2019 (Korean multicentre registry)	4	2	2	8	Moderate
Scholz et al., 2018 (FITT- STEMI)	4	2	3	9	Low
Shiomi et al., 2012 (CREDO-Kyoto)	4	2	2	8	Moderate
Siudak et al., 2017 (ORPKI Poland)	3	2	3	8	Moderate

He et al., 2016 (CAMI registry)	3	2	2	7	Serious
Zhou et al., 2025 (NCPCP China)	4	2	2	8	Moderate
Wang et al., 2022 (Hebei nomogram)	3	2	2	7	Serious
Littnerová et al., 2015 (Brno cohort)	3	2	2	7	Moderate
Şahin et al., 2026 (EASIX cohort)	3	2	2	7	Moderate

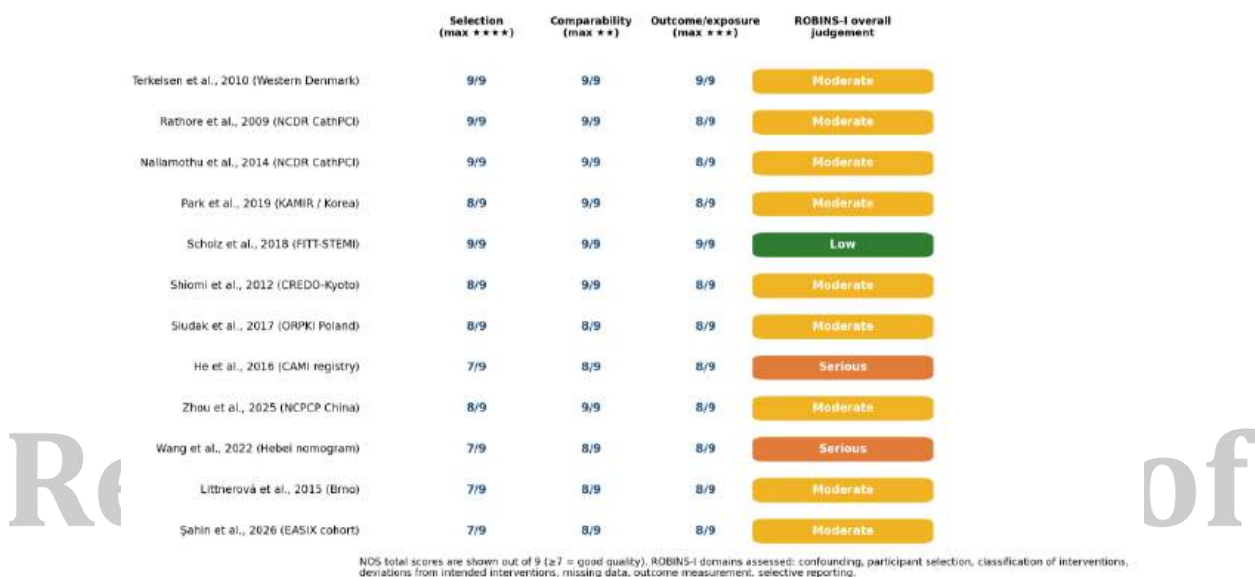


Figure 3. Methodological quality of the twelve non-randomised studies, showing Newcastle–Ottawa Scale scores and the corresponding ROBINS-I overall judgement.

Statistical synthesis

Quantitative pooling was undertaken only where two or more studies compared the same interventions, in comparable populations, using a conceptually equivalent endpoint. Effect estimates were combined on the natural logarithmic scale using DerSimonian–Laird random-effects models, with the between-study variance τ^2 estimated by the method of moments. Statistical heterogeneity was quantified with Cochran's Q and the I^2 statistic, values of I^2 below 25 per cent, between 25 and 75 per cent, and above 75 per cent being interpreted as low, moderate and substantial respectively. Pre-specified subgroup analyses examined the comparator in the

reperfusion comparison (stand-alone fibrinolysis versus a pharmacoinvasive strategy), the method of non-culprit lesion selection (angiographic versus physiological), and the outcome type in the access-site comparison (mortality versus net adverse clinical events). Because the number of studies contributing to any single pooled estimate never exceeded six, formal statistical tests for funnel-plot asymmetry such as Egger's regression were not performed, in accordance with Cochrane guidance that such tests are underpowered when fewer than ten studies are available; a contour-free funnel plot is nevertheless presented for visual inspection. Sensitivity analyses comprised leave-one-out re-estimation, re-analysis under a fixed-effect model, restriction to trials at low risk of bias, and re-expression of the effect on the risk-ratio scale. A two-sided p value below 0.05 was regarded as statistically significant. All computations were performed in Python 3.12 using NumPy and SciPy; no proprietary meta-analytic software was used, and the analytical code is available from the corresponding author on request.

Certainty of the evidence

The certainty of the evidence for each principal outcome was rated using the GRADE approach. Randomised evidence began at high certainty and was downgraded for risk of bias, inconsistency, indirectness, imprecision or suspected publication bias; observational evidence began at low certainty and could be upgraded for a large magnitude of effect, a dose–response gradient, or where all plausible residual confounding would act to reduce the observed effect.

RESULTS

Characteristics of the included studies

The included studies were published between 2009 and 2026 and together enrolled more than 320 000 patients across Europe, North America, East and South-East Asia, the Middle East and Australasia. The twenty-one randomised trials contributed 51 872 randomised patients and the twelve non-randomised studies contributed a further 268 000 patients, the great majority from four large national or multinational registries. Median or mean age ranged from 58 years in CAPTIM to 81 years in TRIANA, the proportion of women ranged from 17 per cent in EXAMINATION to 24 per cent in the CULPRIT-SHOCK cohort, and diabetes mellitus was present in 12 to 20 per cent of participants in the contemporary trials. Follow-up ranged from thirty days to sixteen years, the longest being the extended follow-up of DANAMI-2 and the ten-year follow-up of EXAMINATION.^{1,3,5,18,31,32}

The evidence base is structurally uneven. Six trials and five cohorts addressed reperfusion strategy or reperfusion delay; six trials addressed the completeness and timing of revascularisation; five trials and one registry addressed arterial access; three trial reports addressed thrombus aspiration; four trial reports addressed stent platform; and one trial with two reports addressed the specific problem of cardiogenic shock. The prognostic-model literature was contributed entirely by non-randomised cohorts. No eligible randomised trial was identified that addressed primary PCI in patients presenting more than twelve hours after symptom onset, and none was identified that enrolled exclusively from a low-resource or archipelagic health system comparable to the Indonesian setting.^{35,42,43,44,51}

Table 5. Characteristics of the 33 included studies

Study (year), country	Design	n	Population	Intervention / exposure	Comparator	Follow-up	Principal outcome and key result
Nielsen et al. (2010), Denmark	Multicentre RCT (DANAMI-2)	1 572	STEMI < 12 h, referral and invasive hospitals	Primary PCI with inter-hospital transfer	On-site fibrinolysis (alteplase)	Median 7.8 y	Death or re-infarction 34.8% vs 41.3%; HR 0.78 (0.66–0.92); re-infarction 11.7% vs 18.5%
Thrane et al. (2019), Denmark	Multicentre RCT, extended follow-up (DANAMI-2)	1 572	As above	Primary PCI with inter-hospital transfer	On-site fibrinolysis	16 y	Death or re-hospitalisation for MI 58.7% vs 62.3%; HR 0.86 (0.76–0.98); cardiac death 18.3% vs 22.7%, HR 0.78 (0.63–0.98)
Bueno et al. (2010), Spain	Multicentre RCT (TRIANA)	266	STEMI < 6 h, age ≥ 75 y	Primary PCI	Fibrinolysis	30 d	Death, re-MI or disabling stroke 18.9% vs 25.4%; OR 0.69 (0.38–

	), stopped early		(mean 81 y)				1.23); recurrent ischaemia 0.8% vs 9.7% (p < 0.001)
Armstrong et al. (2013), international	Multicentre RCT (STREAM)	1 892	STEMI < 3 h unable to undergo PCI within 1 h	Primary PCI	Pre-hospital tenecteplase + timely angiography	30 d	Death, shock, congestive heart failure or re-MI 14.3% vs 12.4%; RR 0.86 (0.68–1.09) for fibrinolysis; intracranial haemorrhage 0.2% vs 1.0% (p = 0.04)
Bonnefoy et al. (2009), France	Multicentre RCT (CAPTIM), 5-y follow-up	840	STEMI < 6 h managed pre-hospital	Primary PCI	Pre-hospital alteplase with transfer to a PCI centre	5 y	All-cause death 12.6% vs 9.7%; HR 0.75 (0.50–1.14) for fibrinolysis; in patients treated < 2 h, HR 0.50 (0.25–0.97) favouring fibrinolysis
Thiele et al. (2011), Germany	Multicentre RCT (LIPSIA-STEMI)	162	STEMI < 3 h with long transfer distances	Primary PCI	Pre-hospital tenecteplase-facilitated PCI	30 d	Infarct size 13.7% vs 17.9% of left ventricle (p = 0.10); pre-procedural TIMI 2–3 flow 35% vs 71% (p < 0.001); composite events 13.6% vs 19.8%

Mehta et al. (2019), international	Multicentre RCT (COMPLETE)	4 041	STEMI with multivessel disease after successful culprit PCI	Staged angiography-guided complete revascularisation	Culprit-lesion-only PCI	Median 3 y	CV death or new MI 7.8% vs 10.5%; HR 0.74 (0.60–0.91), p = 0.004; CV death, MI or ischaemia-driven revascularisation HR 0.51 (0.43–0.61)
Wood et al. (2019), international	Pre-specified analysis of COMPLETE	4 041	As above, stratified by planned timing	Non-culprit PCI during index admission (median 1 d) or after discharge (median 23 d)	Culprit-lesion-only PCI	Median 3 y	HR 0.77 (0.59–1.00) in-hospital vs HR 0.69 (0.49–0.97) after discharge; p for interaction = 0.62
Mehta et al. (2022), international	Pre-specified patient-reported outcome analysis of COMPLETE	4 041	As above	Complete revascularisation	Culprit-lesion-only PCI	Median 3 y	Angina-free (SAQ-AF = 100) 87.5% vs 84.3%; absolute difference 3.2% (0.7–5.7), p = 0.01
Engstrøm et al. (2015), Denmark	Multicentre RCT (DANAMI-3-PRIMULTI)	627	STEMI with ≥ 1 significant non-culprit stenosis	FFR-guided complete revascularisation before discharge	Culprit-lesion-only PCI	Median 27 mo	Death, re-MI or ischaemia-driven revascularisation 13% vs 22%; HR 0.56 (0.38–0.83), p = 0.004

Gershlick et al. (2015), United Kingdom	Multicentre RCT (CvLPRIT)	296	STEMI with multivessel disease at primary PCI	In-hospital complete revascularisation	Infarct-related-artery-only PCI	12 mo	Death, re-MI, heart failure or ischaemia-driven revascularisation 10.0% vs 21.2%; HR 0.45 (0.24–0.84), $p = 0.009$
Böhm et al. (2024), international	Registry-based RCT (FULL REVASC)	1 542	STEMI or very-high-risk NSTEMI with multivessel disease	FFR-guided complete revascularisation	Culprit-lesion-only PCI	Median 4.8 y	Death, MI or unplanned revascularisation 19.0% vs 20.4%; HR 0.93 (0.74–1.17), $p = 0.53$
Stähli et al. (2023), Europe	Multicentre non-inferiority RCT (MULTISTARS AMI)	840	Haemodynamically stable STEMI with multivessel disease	Immediate multivessel PCI	Staged multivessel PCI at 19–45 d	1 y	Composite primary endpoint 8.5% vs 16.3%; RR 0.52 (0.38–0.72), $p < 0.001$ for non-inferiority and superiority
Kim et al. (2025), South Korea	Multicentre non-inferiority RCT (OPTION-STEMI)	994	STEMI with multivessel disease after culprit PCI	Immediate complete revascularisation	Staged complete revascularisation during index admission	1 y	Death, non-fatal MI or unplanned revascularisation 13% vs 11%; HR 1.24 (0.86–1.79); non-inferiority not demonstrated ($p = 0.24$)
Park et al. (2023), South Korea	Multicentre RCT, terminated early	248	STEMI with multivessel disease	Immediate complete revascularisation	Staged revascularisation (mean 4.4 d)	12 mo	MACE 11.6% vs 7.5%; HR 1.60 (0.65–3.91); total death 9.7% vs

							2.8%, HR 3.53 (0.97–12.84)
Thiele et al. (2017), Europe	Multicentre RCT (CULPRIT-SHOCK)	706	Acute MI with multivessel disease and cardiogenic shock	Culprit-lesion-only PCI with optional staged revascularisation	Immediate multivessel PCI	30 d	Death or renal-replacement therapy 45.9% vs 55.4%; RR 0.83 (0.71–0.96), p = 0.01; death 43.3% vs 51.5%, RR 0.84 (0.72–0.98)
Thiele et al. (2018), Europe	CULPRIT-SHOCK, 1-year follow-up	706	As above	Culprit-lesion-only PCI	Immediate multivessel PCI	1 y	Death 50.0% vs 56.9%; RR 0.88 (0.76–1.01); repeat revascularisation 32.3% vs 9.4%, RR 3.44 (2.39–4.95)
Romagnoli et al. (2012), Italy	Multicentre RCT (RIFLE-STEACS)	1 001	ST-elevation acute coronary syndrome undergoing primary or rescue PCI	Transradial access	Transfemoral access	30 d	Net adverse clinical events 13.6% vs 21.0% (p = 0.003); cardiac death 5.2% vs 9.2% (p = 0.020); bleeding 7.8% vs 12.2% (p = 0.026)
Bernat et al. (2014), Czech Republic	Multicentre RCT (STEMI-RADIAL)	707	STEMI < 12 h at high-volume radial centres	Transradial access	Transfemoral access	6 mo	Major bleeding / access-site complications 1.4% vs 7.2% (p = 0.0001); NACE 4.6% vs 11.0% (p = 0.0028); death

							2.3% vs 3.1% at 30 d
Le May et al. (2020), Canada	Multicentre RCT (SAFARI-STEMI), stopped for futility	2 292	STEMI referred for primary PCI	Transradial access	Transfemoral access	30 d	All-cause death 1.5% vs 1.3%; RR 1.15 (0.58–2.30), p = 0.69; bleeding 1.4% vs 2.0%, RR 0.71 (0.38–1.33)
Jolly et al. (2011) / Mehta et al. (2012), international	Multicentre RCT (RIVAL) and pre-specified STEMI stratum	7 021 (1 958 STEMI)	Acute coronary syndrome undergoing invasive management	Transradial access	Transfemoral access	30 d	In STEMI: primary composite 3.1% vs 5.2%, HR 0.60 (p = 0.026); all-cause death 1.3% vs 3.2%, HR 0.39 (p = 0.006); no benefit in NSTEMI-ACS
Vranckx et al. (2017), international	Multicentre RCT (MATRI-X), STEMI stratum	8 404 (4 010 STEMI)	Acute coronary syndrome undergoing invasive management	Transradial access	Transfemoral access	30 d	In STEMI: MACE 6.1% vs 6.3%, RR 0.96 (0.75–1.24); NACE 7.2% vs 8.3%, RR 0.86 (0.68–1.08); mortality and access-site bleeding favoured radial in both strata
Fröbert et al. (2013), Sweden / Iceland / Denmark	Registry-based RCT (TASTE)	7 244	STEMI undergoing primary PCI	Manual thrombus aspiration before PCI	PCI alone	30 d	All-cause death 2.8% vs 3.0%; HR 0.94 (0.72–1.22), p = 0.63; stent

							thrombosis 0.2% vs 0.5% (p = 0.06)
Lagerqvist et al. (2014), Sweden / Iceland / Denmark	TASTE, 1-year follow-up	7 244	As above	Manual thrombus aspiration	PCI alone	1 y	All-cause death 5.3% vs 5.6%; HR 0.94 (0.78–1.15); composite of death, re-MI or stent thrombosis 8.0% vs 8.5%, HR 0.94 (0.80–1.11)
Jolly et al. (2016), international	Multicentre RCT (TOTAL), 1-year follow-up	10 732	STEMI < 12 h undergoing primary PCI	Routine manual thrombectomy plus PCI	PCI alone	1 y	Primary composite 8% vs 8%; HR 1.00 (0.87–1.15), p = 0.99; stroke 1.2% vs 0.7%, HR 1.66 (1.10–2.51), p = 0.015
Jolly et al. (2018), international	Pre-specified subgroup of TOTAL	10 732 (high thrombus burden subgroup)	STEMI with TIMI thrombus grade ≥ 3	Routine thrombectomy	PCI alone	1 y	Primary composite 8.1% vs 8.3%; HR 0.97 (0.84–1.13); 30-day stroke 0.7% vs 0.4%, HR 1.90 (1.04–3.48)
Sabaté et al. (2016), Spain / Italy / Netherlands	Multicentre RCT (EXAMINATION), 5-y follow-up	1 498	All-comer STEMI < 48 h requiring emergent PCI	Everolimus-eluting stent	Cobalt-chromium bare-metal stent	5 y	Patient-oriented composite 21% vs 26%; HR 0.80 (0.65–0.98), p = 0.033; all-cause death 9% vs 12%, HR 0.72, p = 0.047

Brugaletta et al. (2021), Spain / Italy / Netherlands	EXAMINATION-EXTEND, 10-y follow-up	1 498	As above	Everolimus-eluting stent	Bare-metal stent	10 y	Patient-oriented composite 32.4% vs 38.0%, HR 0.81 (0.68–0.96), p = 0.013; device-oriented composite 13.6% vs 18.4%, HR 0.72 (0.55–0.93); definite stent thrombosis 2.2% vs 2.5%
Iglesias et al. (2019), Switzerland	Multicentre single-blind RCT (BIOSTEMI)	1 300	STEMI < 24 h undergoing primary PCI	Ultrathin biodegradable-polymer sirolimus-eluting stent	Durable-polymer everolimus-eluting stent	12 mo	Target-lesion failure 4% vs 6%; RR 0.59 (95% BCI 0.37–0.94); posterior probability of superiority 0.986
Pilgrim et al. (2021), Switzerland	BIOSTEMI, final 2-year outcomes	1 300	As above	Biodegradable-polymer sirolimus-eluting stent	Durable-polymer everolimus-eluting stent	2 y	Target-lesion failure 5.1% vs 8.1%; RR 0.58 (95% BCI 0.40–0.84); clinically indicated TLR 2.5% vs 5.1%, RR 0.52 (0.30–0.87)
Terkelsen et al. (2010), Denmark	Population-based historical follow-up cohort	6 209	STEMI transported by emergency medical services and treated with	System delay 0–360 min (continuous exposure)	Shortest delay stratum (0–60 min)	Median 3.4 y	Long-term mortality 15.4%, 23.3%, 28.1% and 30.8% across increasing delay strata (p < 0.001); adjusted HR 1.10

			primary PCI < 12 h				(1.04–1.16) per additional hour
Rathore et al. (2009), United States	Prospecti ve national registry cohort (NCDR)	43 801	STEMI undergoin g primary PCI	Door-to-balloon time (continuous)	Shorter door- to-balloon time	In hospital	Adjusted in- hospital mortality rose continuously from 3.0% at 30 min to 8.4% at 180 min ($p < 0.001$); overall mortality 4.6%
Nallamothe et al. (2014), United States	Retrospec tive national registry cohort (NCDR)	150 116	STEMI undergoin g primary PCI, 2005– 2011	Patient-specific door-to-balloon time	Longer door- to-balloon time	In hospital and 6 mo	Adjusted OR 0.92 (0.91–0.93) for in- hospital death and 0.94 (0.93–0.95) for 6-month death per 10-min reduction, despite rising population- level risk
Park et al. (2019), South Korea	Multicent re prospectiv e registry cohort	5 243	STEMI treated with primary PCI at 20 tertiary centres	Door-to-balloon and onset-to-door time	Longer time intervals	1 y	Adjusted HR 1.90 (1.51–2.39) per 1- h increase in door- to-balloon time; door-to-balloon < 45 min vs > 90 min, adjusted HR 0.30 (0.19–0.42)
Scholz et al. (2018), Germany	Prospecti ve multicentr e cohort (FITT- STEMI)	12 675	STEMI transporte d by emergency medical services	Contact-to-balloon time, stratified by shock and cardiac arrest	Shorter contact-to- balloon time	In hospital	Near-linear delay– mortality relation; every 10-min delay caused 3.31 additional deaths per 100 patients in

			and treated with primary PCI				cardiogenic shock vs 0.34 in stable patients ($p < 0.0001$)
Shiomi et al. (2012), Japan	Multicentre observational cohort (CREDO-Kyoto)	3 391	STEMI treated with primary PCI < 24 h	Onset-to-balloon time ≤ 3 h	Onset-to-balloon time > 3 h	3 y	Death or congestive heart failure 13.5% vs 19.2% ($p < 0.001$); adjusted HR 0.70 (0.56–0.88); door-to-balloon benefit confined to early presenters
Siudak et al. (2017), Poland	National registry cohort with propensity-score analysis (ORPKI)	22 812	Consecutive STEMI treated with PCI and stenting at 151 centres	Transradial approach	Transfemoral approach	Peri-procedural	Peri-procedural death 0.93% vs 1.94% ($p = 0.001$); access-site bleeding after PCI 0.09% vs 0.23% ($p = 0.049$)
He et al. (2016), China	National prospective registry cohort (CAMI)	Elderly STEMI subset	STEMI patients aged ≥ 75 years	Primary PCI	Fibrinolysis or no reperfusion	In hospital	In-hospital death 7.7% (primary PCI), 15.0% (fibrinolysis) and 19.9% (no reperfusion), $p < 0.001$; lower rates of heart failure, mechanical complications and cardiac arrest with primary PCI

Zhou et al. (2025), China	Quasi-experimental propensity-matched national registry (NCPCP)	19334 matched	STEMI treated between 2016 and 2022	Primary PCI	On-site fibrinolysis	In hospital	Mortality 2.34% vs 6.01% when PCI-related delay < 60 min; benefit lost beyond 90 min; equipoise threshold 119.5 min
Wang et al. (2022), China	Multicentre retrospective observational study	855	STEMI undergoing primary PCI at 39 hospitals	Ten-variable prognostic nomogram	Conventional clinical assessment	In hospital	AUC 0.947 (0.927–0.967) in the training set and 0.891 (0.844–0.939) in the testing set; in-hospital death 223/855
Littnerová et al. (2015), Czech Republic	Prospective single-centre cohort	593	STEMI treated with primary PCI	Six established risk scores (TIMI, dynamic TIMI, CADILLAC, PAMI, Zwolle, GRACE)	Comparison between scores	≥ 3 y	AUC 0.73–0.85 for 6- and 12-month mortality; GRACE best for long-term mortality; Zwolle best for heart-failure re-hospitalisation (AUC 0.80–0.83)
Şahin et al. (2026), Türkiye	Retrospective single-centre cohort	1931	STEMI treated with primary PCI, 2023–2025	Admission Endothelial Activation and Stress Index (EASIX)	Lower EASIX values	In hospital	No-reflow 14.1% and in-hospital mortality 2.5%; adjusted OR 1.485 (1.286–1.715) for no-reflow; ROC-AUC 0.706 for no-

							reflow and 0.810 for mortality
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RCT = randomised controlled trial; CV = cardiovascular; MI = myocardial infarction; FFR = fractional flow reserve; NACE = net adverse clinical events; TLR = target-lesion revascularisation; SAQ-AF = Seattle Angina Questionnaire angina-frequency score; BCI = Bayesian credible interval; AUC = area under the receiver-operating-characteristic curve; IQR = interquartile range. Where several reports of the same randomised cohort are listed, the cohort contributed only once to any pooled estimate.

Short-term all-cause mortality

Short-term mortality was reported by twenty-two of the thirty-three included studies. In the randomised comparison of primary PCI with stand-alone fibrinolysis, the two eligible trials produced concordant estimates and pooled to a statistically significant advantage for primary PCI, with an estimate of 0.85 (95% confidence interval 0.75 to 0.96), no detectable heterogeneity ($I^2 = 0$ per cent, $\tau^2 = 0.000$) and a two-sided p value of 0.011. In the TRIANA trial, restricted to patients aged seventy-five years or older with a mean age of eighty-one, the composite of death, re-infarction or disabling stroke occurred in 18.9 per cent of patients allocated to primary PCI and 25.4 per cent of those allocated to fibrinolysis, an odds ratio of 0.69 (0.38 to 1.23) that did not reach conventional significance in a trial stopped early for slow recruitment, although recurrent ischaemia was reduced almost twelvefold, from 9.7 per cent to 0.8 per cent ($p < 0.001$).^{1,3}

The observational evidence generated in the modern era produced a considerably larger estimate of benefit, but only within a narrow window of procedural delay. In the Chinese National Chest Pain Center Program, 19 334 propensity-matched patients treated between 2016 and 2022 experienced in-hospital mortality of 2.34 per cent after primary PCI and 6.01 per cent after on-site fibrinolysis when the PCI-related delay was less than sixty minutes, corresponding to an odds ratio computed from the reported event rates of 0.38 (0.32 to 0.44; $p < 0.001$). That advantage diminished progressively as delay lengthened and was lost entirely once the difference between door-to-wire and door-to-needle time exceeded 119.5 minutes. The Chinese Acute Myocardial Infarction registry produced a directionally identical result in patients aged seventy-five years and over, with in-hospital death occurring in 7.7 per cent of those treated with primary PCI, 15.0 per

cent of those treated with fibrinolysis and 19.9 per cent of those who received no reperfusion at all ($p < 0.001$).^{42,43}

Table 6. Short-term (in-hospital or 30-day) all-cause mortality

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Thiele et al. (2017)	Culprit-only vs immediate multivessel PCI in cardiogenic shock	Death 149/344 (43.3%)	Death 176/341 (51.5%)	RR 0.84 (0.72–0.98)	0.03
Bueno et al. (2010)	Primary PCI vs fibrinolysis, age ≥ 75 y	18/134 (13.6%)	23/132 (17.2%)	OR 0.69 (0.38–1.23)*	0.43
Fröbert et al. (2013)	Thrombus aspiration vs PCI alone	103/3 621 (2.8%)	110/3 623 (3.0%)	HR 0.94 (0.72–1.22)	0.63
Le May et al. (2020)	Radial vs femoral access	17/1 136 (1.5%)	15/1 156 (1.3%)	RR 1.15 (0.58–2.30)	0.69
Mehta et al. (2012)	Radial vs femoral access, STEMI stratum	1.3%	3.2%	HR 0.39	0.006
Bernat et al. (2014)	Radial vs femoral access	8/348 (2.3%)	11/359 (3.1%)	OR 0.74 (0.30–1.87)*	0.64
Zhou et al. (2025)	Primary PCI vs on-site fibrinolysis, delay < 60 min	2.34%	6.01%	OR 0.38 (0.32–0.44)*	< 0.001
He et al. (2016)	Primary PCI vs fibrinolysis vs no reperfusion, age ≥ 75 y	7.7%	15.0% and 19.9%	Adjusted analysis favouring primary PCI	< 0.001
Rathore et al. (2009)	Door-to-balloon time gradient	3.0% at 30 min	8.4% at 180 min	Continuous non-linear association	< 0.001

Siudak et al. (2017)	Radial vs femoral access	0.93%	1.94%	Propensity-matched comparison	0.001
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**Odds ratio computed by the reviewers from the event counts or event rates and group sizes reported in the source publication; for propensity-matched cohorts equal allocation between matched groups was assumed.*

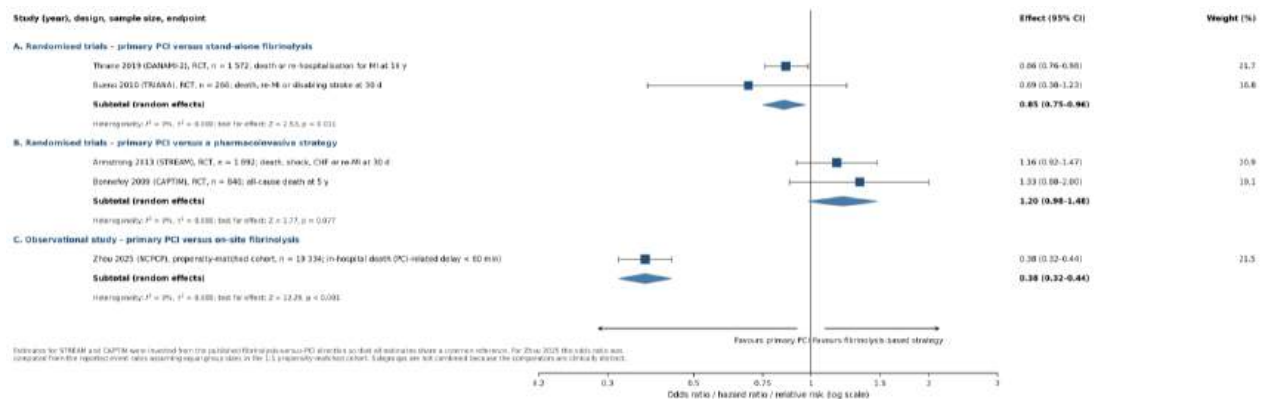


Figure 4. Subgrouped forest plot of reperfusion strategy in STEMI. Subgroup A compares primary PCI with stand-alone fibrinolysis, subgroup B compares primary PCI with a pharmacoinvasive strategy, and subgroup C presents the contemporary observational comparison. Subgroups are not combined because the comparators are clinically distinct.

Long-term all-cause mortality

Long-term mortality data were available from ten studies, with follow-up extending to sixteen years. The sixteen-year report of DANAMI-2 found no significant difference in all-cause mortality between primary PCI and fibrinolysis in the overall cohort, but a sustained reduction in the composite of death or re-hospitalisation for myocardial infarction, which occurred in 58.7 per cent of the primary PCI group and 62.3 per cent of the fibrinolysis group (hazard ratio 0.86, 0.76 to 0.98). Among the subgroup transported from referral hospitals the corresponding hazard ratio was 0.82 (0.71 to 0.96), and primary PCI postponed the occurrence of a main event by an average of 12.3 months (5.0 to 19.5). At the earlier eight-year analysis, mortality among patients randomised at referral hospitals was 26.7 per cent after primary PCI and 33.3 per cent after fibrinolysis (hazard ratio 0.78, 0.63 to 0.97), demonstrating that the survival advantage is concentrated in precisely the population for whom the logistics of transfer are most demanding.^{1,2}

The five-year follow-up of CAPTIM points in the opposite direction and is instructive. All-cause mortality was 9.7 per cent after pre-hospital fibrinolysis and 12.6 per cent after primary angioplasty, a non-significant difference overall (hazard ratio 0.75, 0.50 to 1.14), but among patients randomised within two hours of symptom onset mortality was 5.8 per cent with pre-hospital fibrinolysis and 11.1 per cent with primary angioplasty (hazard ratio 0.50, 0.25 to 0.97; $p = 0.04$). A pooled analysis of individual data from CAPTIM and WEST confirmed a significant interaction between presentation delay and treatment allocation ($p = 0.043$), with fibrinolysis superior below two hours and no difference thereafter. Long-term mortality was also reduced by stent choice: in EXAMINATION, all-cause death at five years occurred in 9 per cent of patients receiving an everolimus-eluting stent and 12 per cent of those receiving a bare-metal stent (hazard ratio 0.72; $p = 0.047$).^{5,6,31}

Table 7. Long-term all-cause mortality

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Thrane et al. (2019)	Primary PCI vs fibrinolysis, 16 y	All-cause death: no significant difference	Reference	HR for death or re-hospitalisation for MI 0.86 (0.76–0.98)	0.02
Nielsen et al. (2010)	Primary PCI vs fibrinolysis, 8 y (referral hospitals)	26.7%	33.3%	HR 0.78 (0.63–0.97)	< 0.05
Bonnefoy et al. (2009)	Primary PCI vs pre-hospital fibrinolysis, 5 y	12.6%	9.7%	HR 0.75 (0.50–1.14) favouring fibrinolysis	0.18
Sabaté et al. (2016)	Everolimus-eluting vs bare-metal stent, 5 y	65/751 (9%)	88/747 (12%)	HR 0.72 (0.52–1.00)	0.047

Brugaletta et al. (2021)	Everolimus-eluting vs bare-metal stent, 10 y	Patient-oriented composite 32.4%	38.0%	HR 0.81 (0.68–0.96)	0.013
Lagerqvist et al. (2014)	Thrombus aspiration vs PCI alone, 1 y	191/3 621 (5.3%)	202/3 623 (5.6%)	HR 0.94 (0.78–1.15)	0.57
Thiele et al. (2018)	Culprit-only vs multivessel PCI in shock, 1 y	172/344 (50.0%)	194/341 (56.9%)	RR 0.88 (0.76–1.01)	Not significant
Böhm et al. (2024)	FFR-guided complete vs culprit-only, 4.8 y	145/764 (19.0%) for the composite	159/778 (20.4%)	HR 0.93 (0.74–1.17)	0.53
Terkelsen et al. (2010)	System delay, median 3.4 y	15.4% (0–60 min)	30.8% (181–360 min)	Adjusted HR 1.10 (1.04–1.16) per hour	< 0.001
Nallamothu et al. (2014)	Door-to-balloon time, 6 mo	Per 10-min reduction	Reference	Adjusted OR 0.94 (0.93–0.95)	< 0.0001

Cardiovascular and cardiac mortality

Eight studies reported adjudicated cardiac or cardiovascular death. The clearest signal came from the extended follow-up of DANAMI-2, in which cardiac mortality was reduced in absolute terms by 4.4 percentage points, from 22.7 per cent to 18.3 per cent (hazard ratio 0.78, 0.63 to 0.98), notwithstanding the absence of a difference in all-cause mortality — a dissociation that indicates the benefit of mechanical reperfusion is specific to the cardiac cause of death and is progressively diluted over sixteen years by competing non-cardiac mortality. In COMPLETE, the coprimary composite of cardiovascular death or new myocardial infarction occurred in 7.8 per cent of patients assigned to complete revascularisation and 10.5 per cent assigned to culprit-lesion-only PCI (hazard ratio 0.74, 0.60 to 0.91; $p = 0.004$). In RIFLE-STEACS, cardiac death at thirty days was 5.2 per cent with radial access and 9.2 per cent with femoral access ($p = 0.020$), an effect of a magnitude that has never been reproduced in a subsequent access-site trial and that must be interpreted in the light of that trial's high risk-of-bias rating.^{1,8,20}

Table 8, Cardiovascular and cardiac mortality

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Thrane et al. (2019)	Primary PCI vs fibrinolysis, 16 y	Cardiac death 18.3%	22.7%	HR 0.78 (0.63–0.98)	< 0.05
Mehta et al. (2019)	Complete vs culprit-only revascularisation	CV death or MI 158/2 016 (7.8%)	213/2 025 (10.5%)	HR 0.74 (0.60–0.91)	0.004
Romagnoli et al. (2012)	Radial vs femoral access	Cardiac death 26/500 (5.2%)	46/501 (9.2%)	OR 0.54 (0.33–0.89)*	0.020
Jolly et al. (2016)	Thrombectomy vs PCI alone, 1 y	CV death 179/5 035 (4%)	192/5 029 (4%)	HR 0.93 (0.76–1.14)	0.48
Jolly et al. (2018)	Thrombectomy in high thrombus burden, 1 y	CV death	Reference	HR 0.88 (0.72–1.09)	0.25
Brugaletta et al. (2021)	Everolimus-eluting vs bare-metal stent, 10 y	Device-oriented composite 13.6%	18.4%	HR 0.72 (0.55–0.93)	0.012
Iglesias et al. (2019)	Biodegradable- vs durable-polymer stent	Cardiac death	Reference	No significant difference at 12 mo	Not significant
Bueno et al. (2010)	Primary PCI vs fibrinolysis, age $\geq$ 75 y	Death 13.6%	17.2%	Pooled OR with previous elderly trials 0.64 (0.45–0.91)	< 0.05

Recurrent myocardial infarction

Recurrent infarction was the outcome on which mechanical reperfusion demonstrated its most consistent and durable advantage. In DANAMI-2 at eight years, re-infarction occurred in 11.7 per cent of the primary PCI group and 18.5 per cent of the fibrinolysis group, a hazard ratio of 0.60 (0.46 to 0.77) representing a relative reduction of forty per cent that is attributable to the definitive mechanical treatment of the culprit stenosis rather than to the transient restoration of

patency achieved by lysis. Among patients randomised at referral hospitals the hazard ratio was 0.66 (0.49 to 0.89). In the complete-revascularisation trials, reduction of new myocardial infarction was the principal driver of the composite benefit observed in COMPLETE, whereas in DANAMI-3-PRIMULTI the benefit was driven almost entirely by repeat revascularisation rather than by re-infarction, all-cause mortality and non-fatal re-infarction being statistically indistinguishable between arms.^{2,8,12}

Table 9. Recurrent myocardial infarction

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Nielsen et al. (2010)	Primary PCI vs fibrinolysis, 8 y	11.7%	18.5%	HR 0.60 (0.46–0.77)	< 0.001
Mehta et al. (2019)	Complete vs culprit-only revascularisation	New MI (component of coprimary outcome)	Reference	HR 0.74 (0.60–0.91) for CV death or MI	0.004
Engstrøm et al. (2015)	FFR-guided complete vs culprit-only	Non-fatal re-infarction	Reference	No significant difference; benefit driven by revascularisation	Not significant
Armstrong et al. (2013)	Pharmacoinvasive vs primary PCI	Re-infarction within the composite	Reference	RR 0.86 (0.68–1.09) for the composite	0.21
Lagerqvist et al. (2014)	Thrombectomy vs PCI alone, 1 y	2.7%	2.7%	HR 0.97 (0.73–1.28)	0.81
Thiele et al. (2018)	Culprit-only vs multivessel PCI in shock, 1 y	1.7%	2.1%	RR 0.85 (0.29–2.50)	Not significant
Bueno et al. (2010)	Primary PCI vs fibrinolysis, elderly	5.3%	8.2%	Absolute difference –2.9%	0.35

Sabaté et al. (2016)	Everolimus-eluting vs bare-metal stent, 1 y	10/751 (1.3%)	15/747 (2.0%)	Not significant	0.32
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Stroke and intracranial haemorrhage

Stroke was reported by eight studies and produced the single most important safety signal in this review. In the one-year analysis of TOTAL, stroke occurred in 1.2 per cent of patients randomised to routine manual thrombectomy and 0.7 per cent of those randomised to PCI alone (hazard ratio 1.66, 1.10 to 2.51; $p = 0.015$), a finding sufficiently robust that the investigators concluded thrombus aspiration could no longer be recommended as a routine strategy. Within the pre-specified subgroup of patients with a Thrombolysis in Myocardial Infarction thrombus grade of three or more — the very group in which benefit had been anticipated on mechanistic grounds — thirty-day stroke was more frequent with thrombectomy (0.7 per cent versus 0.4 per cent; hazard ratio 1.90, 1.04 to 3.48) while the primary composite was unchanged. Conversely, the haemorrhagic hazard of pharmacological reperfusion was confirmed in STREAM, in which intracranial haemorrhage occurred in 1.0 per cent of the fibrinolysis group and 0.2 per cent of the primary PCI group ($p = 0.04$), an excess that fell to 0.5 per cent versus 0.3 per cent after the protocol was amended to halve the tenecteplase dose in patients aged seventy-five years or older.^{4,29,30}

Table 10. Stroke, transient ischaemic attack and intracranial haemorrhage

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Jolly et al. (2016)	Thrombectomy vs PCI alone, 1 y	60/5 035 (1.2%)	36/5 029 (0.7%)	HR 1.66 (1.10–2.51)	0.015
Jolly et al. (2018)	Thrombectomy in high thrombus burden, 30 d	31 (0.7%)	16 (0.4%)	HR 1.90 (1.04–3.48)	< 0.05
Armstrong et al. (2013)	Pharmacoinvasive vs primary PCI	Intracranial haemorrhage 1.0%	0.2%	Absolute excess 0.8%	0.04

Bueno et al. (2010)	Primary PCI vs fibrinolysis, elderly	Disabling stroke 0.8%	3.0%	Absolute difference –2.2%	0.18
Fröbert et al. (2013)	Thrombectomy vs PCI alone, discharge	Stroke or neurological complication 0.5%	0.5%	No difference	0.87
Le May et al. (2020)	Radial vs femoral access	1.0%	0.4%	RR 2.24 (0.78–6.42)	0.12
Vranckx et al. (2017)	Radial vs femoral access, STEMI stratum	Stroke component of MACE	Reference	RR 0.96 (0.75–1.24) for MACE	0.76
Stähli et al. (2023)	Immediate vs staged multivessel PCI	Stroke	Reference	Risks appeared similar between groups	Not significant

Major bleeding

Major bleeding and access-site vascular complications were reported by eight studies and constitute the domain in which transradial access demonstrates its most consistent and least disputed advantage. In STEMI-RADIAL, the composite of major bleeding and access-site complications occurred in 1.4 per cent of the radial group and 7.2 per cent of the femoral group ($p = 0.0001$), an absolute reduction of 5.8 percentage points corresponding to a number needed to treat of seventeen. In RIFLE-STEACS the corresponding rates were 7.8 per cent and 12.2 per cent ($p = 0.026$). SAFARI-STEMI, which was stopped early for futility after enrolling 2 292 patients, found bleeding rates of 1.4 per cent and 2.0 per cent respectively (relative risk 0.71, 0.38 to 1.33), a non-significant difference that must be interpreted in the context of a trial in which 88 to 92 per cent of patients received bivalirudin and 68 per cent of femoral procedures used a vascular closure device — a degree of bleeding-avoidance co-intervention that is not representative of routine practice in most health systems.^{20,21,22}

Table 11. Major bleeding and access-site vascular complications

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Romagnoli et al. (2012)	Radial vs femoral access	7.8%	12.2%	Absolute difference –4.4%	0.026
Bernat et al. (2014)	Radial vs femoral access	Major bleeding / access-site complication 1.4%	7.2%	Absolute difference –5.8%	0.0001
Le May et al. (2020)	Radial vs femoral access	1.4%	2.0%	RR 0.71 (0.38–1.33)	0.28
Jolly et al. (2011)	Radial vs femoral access (whole RIVAL cohort)	24/3 507 (0.7%)	33/3 514 (0.9%)	HR 0.73 (0.43–1.23)	0.23
Siudak et al. (2017)	Radial vs femoral access	Access-site bleeding after PCI 0.09%	0.23%	Propensity-matched comparison	0.049
Thiele et al. (2017)	Culprit-only vs multivessel PCI in shock	Bleeding rates	Reference	No significant difference between groups	Not significant
Sabaté et al. (2016)	Everolimus-eluting vs bare-metal stent, 1 y	29/751 (3.9%)	39/747 (5.2%)	Not significant	0.19
Pilgrim et al. (2021)	Biodegradable- vs durable-polymer stent, 2 y	BARC 3–5 bleeding	Reference	No significant difference	Not significant

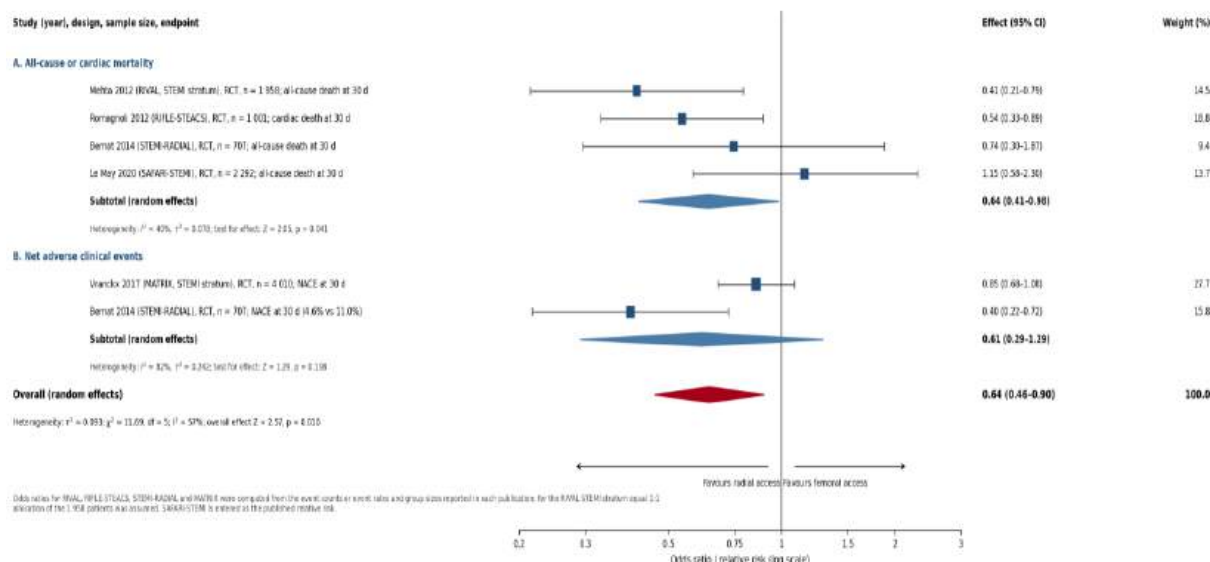


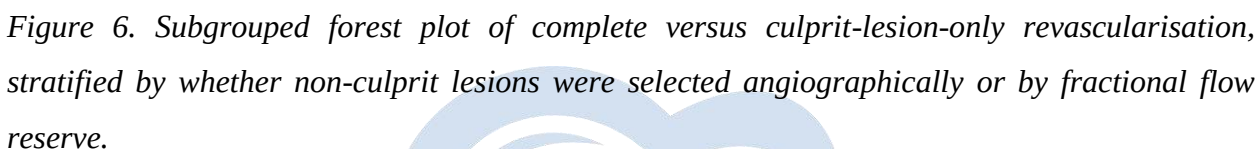
Figure 5. Subgrouped forest plot of transradial versus transfemoral arterial access for primary PCI in STEMI, showing the mortality subgroup, the net-adverse-clinical-events subgroup and the overall random-effects estimate.

Repeat and unplanned revascularisation

Repeat revascularisation was reported by eight studies and yielded the largest and most reproducible treatment effects in the entire review. In COMPLETE, the second coprimary composite of cardiovascular death, myocardial infarction or ischaemia-driven revascularisation occurred in 8.9 per cent of the complete-revascularisation group and 16.7 per cent of the culprit-lesion-only group, a hazard ratio of 0.51 (0.43 to 0.61; $p < 0.001$). In DANAMI-3-PRIMULTI the primary composite fell from 22 per cent to 13 per cent (hazard ratio 0.56, 0.38 to 0.83), an effect the investigators attributed explicitly to fewer repeat revascularisations rather than to any reduction in death or re-infarction, and in CvLPRIT the composite fell from 21.2 per cent to 10.0 per cent (hazard ratio 0.45, 0.24 to 0.84). The number needed to treat to prevent one repeat revascularisation has been estimated at eight in a contemporaneous meta-analysis, compared with seventy to prevent one cardiovascular death. In the opposite direction, the culprit-only strategy that reduced thirty-day death in cardiogenic shock produced a more than threefold increase in repeat revascularisation at one year, from 9.4 per cent to 32.3 per cent (relative risk 3.44, 2.39 to 4.95).^{8,12,13,19,57}

Table 12. Repeat, unplanned and target-lesion revascularisation

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Mehta et al. (2019)	Complete vs culprit-only revascularisation	CV death, MI or ischaemia-driven revascularisation 8.9%	16.7%	HR 0.51 (0.43–0.61)	< 0.001
Engstrøm et al. (2015)	FFR-guided complete vs culprit-only	13%	22%	HR 0.56 (0.38–0.83); driven by repeat revascularisation	0.004
Gershlick et al. (2015)	Complete vs infarct-related-artery-only PCI	10.0%	21.2%	HR 0.45 (0.24–0.84)	0.009
Thiele et al. (2018)	Culprit-only vs multivessel PCI in shock, 1 y	32.3%	9.4%	RR 3.44 (2.39–4.95)	< 0.001
Brugaletta et al. (2021)	Everolimus-eluting vs bare-metal stent, 10 y	Target-lesion revascularisation 5.7%	8.8%	Absolute difference –3.1%	0.018
Sabaté et al. (2012/2016)	Everolimus-eluting vs bare-metal stent, 1 y	TLR 16/751 (2.1%)	37/747 (5.0%)	Absolute difference –2.9%	0.003
Pilgrim et al. (2021)	Biodegradable- vs durable-polymer stent, 2 y	Clinically indicated TLR 2.5%	5.1%	RR 0.52 (95% BCI 0.30–0.87)	Posterior probability 0.993
Stähli et al. (2023)	Immediate vs staged multivessel PCI	Unplanned ischaemia-driven revascularisation 4.1%	9.3%	Component of RR 0.52 (0.38–0.72)	< 0.001



Stent thrombosis

Table 13. Definite and definite/probable stent thrombosis

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Sabaté et al. (2012/2016)	Everolimus-eluting vs bare-metal stent, 1 y	Definite 4/751 (0.5%)	14/747 (1.9%)	Absolute difference –1.4%	0.019
Brugaletta et al. (2021)	Everolimus-eluting vs bare-metal stent, 10 y	Definite 2.2%	2.5%	No significant difference	0.590
Iglesias et al. (2019)	Biodegradable- vs durable-polymer stent, 1 y	Definite stent thrombosis	Reference	No significant difference	Not significant
Fröbert et al. (2013)	Thrombectomy vs PCI alone, 30 d	0.2%	0.5%	HR 0.47 (0.20–1.02)	0.06
Lagerqvist et al. (2014)	Thrombectomy vs PCI alone, 1 y	0.7%	0.9%	HR 0.84 (0.50–1.40)	0.51
Angerås et al. (2018)	Thrombectomy vs PCI alone (SCAAR registry)	Risk reduction –2.7% at 30 d	Reference	95% CI –4.1 to –1.4	< 0.001
Bangalore et al. (2013)	Everolimus-eluting stent vs bare-metal stent (trial-level network)	Any stent thrombosis	Reference	RR 0.42 (95% CrI 0.23–0.76)	Credible interval excludes 1

Heart failure and cardiogenic shock

Heart failure and cardiogenic shock were reported by eight studies. The most consequential finding concerns the interaction between reperfusion delay and haemodynamic state. In the FITT-STEMI programme, which analysed 12 675 patients transported by emergency medical services, the relationship between contact-to-balloon time and mortality was near-linear between sixty and one hundred and eighty minutes in all strata, but its slope differed profoundly: among patients in cardiogenic shock without cardiac arrest, every additional ten minutes of delay produced 3.31 additional deaths per hundred patients treated, compared with 2.09 among those with shock and arrest, 1.34 among those with arrest alone and 0.34 among haemodynamically stable patients ($p < 0.0001$ for the difference between strata). In CREDO-Kyoto, an onset-to-balloon time of three hours or less was associated with a composite of death or congestive heart failure of 13.5 per cent compared with 19.2 per cent beyond three hours (adjusted hazard ratio 0.70, 0.56 to 0.88). At one

year in CULPRIT-SHOCK, re-hospitalisation for heart failure was more common in the culprit-only arm (5.2 per cent versus 1.2 per cent; relative risk 4.46, 1.53 to 13.04), the price paid for the early mortality advantage of the more conservative strategy.^{19,39,40}

Table 14. Heart failure and cardiogenic shock

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Thiele et al. (2018)	Culprit-only vs multivessel PCI in shock, 1 y	Re-hospitalisation for heart failure 5.2%	1.2%	RR 4.46 (1.53–13.04)	< 0.05
Jolly et al. (2016)	Thrombectomy vs PCI alone	Heart failure component of the composite	Reference	No difference in the composite, HR 1.00 (0.87–1.15)	0.99
Armstrong et al. (2013)	Pharmacoinvasive vs primary PCI	Shock and congestive heart failure within composite	Reference	RR 0.86 (0.68–1.09)	0.21
Shiomi et al. (2012)	Onset-to-balloon ≤ 3 h vs > 3 h	Death or congestive heart failure 13.5%	19.2%	Adjusted HR 0.70 (0.56–0.88)	0.002
Kim et al. (2025)	Immediate vs staged complete revascularisation	In-hospital cardiogenic shock 18/498 (4%)	9/496 (2%)	Numerically higher with immediate PCI	Not formally tested
He et al. (2016)	Primary PCI vs fibrinolysis vs no reperfusion, elderly	Lower rates of heart failure, mechanical complications	Reference	Multivariable adjustment	< 0.05

		and cardiac arrest			
Scholz et al. (2018)	Contact-to-balloon delay in cardiogenic shock	3.31 additional deaths per 100 patients per 10-min delay	0.34 in stable patients	Difference across strata	< 0.0001
Littnerová et al. (2015)	Risk scores for heart-failure re-hospitalisation	Zwolle score	Other scores	AUC 0.80–0.83 up to 2 y	< 0.05

Composite MACE and net adverse clinical events

Composite endpoints were reported by every included randomised trial. Two findings deserve emphasis. First, the timing of complete revascularisation produced diametrically opposed results in two contemporaneous non-inferiority trials: MULTISTARS AMI found immediate multivessel PCI to be not merely non-inferior but superior to staged PCI performed nineteen to forty-five days later (8.5 per cent versus 16.3 per cent; relative risk 0.52, 0.38 to 0.72; $p < 0.001$), whereas OPTION-STEMI, which compared immediate PCI with staged PCI performed on another day during the same admission, failed to demonstrate non-inferiority (13 per cent versus 11 per cent; hazard ratio 1.24, 0.86 to 1.79; p for non-inferiority 0.24) and recorded numerically more in-hospital cardiogenic shock in the immediate arm (4 per cent versus 2 per cent). The two trials are reconcilable if the relevant comparison is not immediate versus staged but rather early versus late, since the disadvantage in MULTISTARS AMI accrued to patients who waited weeks and were exposed to an untreated non-culprit lesion in the interim. Second, in the access-site literature the composite net adverse clinical events endpoint favoured radial access in the two trials conducted exclusively in STEMI (13.6 per cent versus 21.0 per cent in RIFLE-STEACS; 4.6 per cent versus 11.0 per cent in STEMI-RADIAL) but not in the STEMI stratum of MATRIX (7.2 per cent versus 8.3 per cent; relative risk 0.86, 0.68 to 1.08).^{15,16,20,21,25}

Table 15. Composite MACE and net adverse clinical events

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value

Romagnoli et al. (2012)	Radial vs femoral access	NACE 68/500 (13.6%)	105/501 (21.0%)	Absolute difference –7.4%	0.003
Bernat et al. (2014)	Radial vs femoral access	NACE 4.6%	11.0%	Absolute difference –6.4%	0.0028
Vranckx et al. (2017)	Radial vs femoral access, STEMI stratum	NACE 142/2001 (7.2%)	165/2009 (8.3%)	RR 0.86 (0.68–1.08)	0.18
Mehta et al. (2012)	Radial vs femoral access, STEMI stratum	Primary composite 3.1%	5.2%	HR 0.60	0.026
Stähli et al. (2023)	Immediate vs staged multivessel PCI	35/418 (8.5%)	68/422 (16.3%)	RR 0.52 (0.38–0.72)	< 0.001
Kim et al. (2025)	Immediate vs staged complete revascularisation	65/498 (13%)	53/496 (11%)	HR 1.24 (0.86–1.79)	0.24 (non-inferiority)
Gershlick et al. (2015)	Complete vs infarct-related-artery-only PCI	10.0%	21.2%	HR 0.45 (0.24–0.84)	0.009
Iglesias et al. (2019)	Biodegradable- vs durable-polymer stent	Target-lesion failure 25/649 (4%)	36/651 (6%)	RR 0.59 (95% BCI 0.37–0.94)	Posterior probability 0.986
Sabaté et al. (2016)	Everolimus-eluting vs bare-metal stent, 5 y	159/751 (21%)	192/747 (26%)	HR 0.80 (0.65–0.98)	0.033

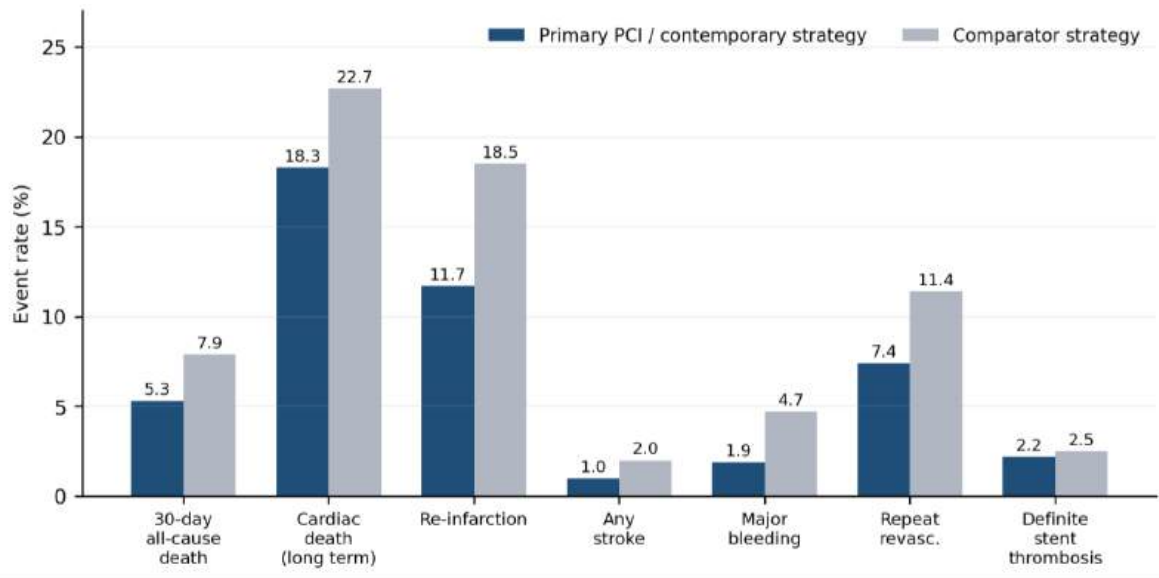


Figure 7. Representative event rates across the principal outcome domains, drawn from the long-term reports of the included trials to illustrate the relative magnitude of each outcome.

Renal outcomes

Renal outcomes were reported by eight studies. In CULPRIT-SHOCK, the composite primary endpoint of death or severe renal failure requiring renal-replacement therapy occurred in 45.9 per cent of the culprit-lesion-only group and 55.4 per cent of the immediate multivessel PCI group (relative risk 0.83, 0.71 to 0.96; $p = 0.01$); the renal component alone showed a relative risk of 0.71 (0.49 to 1.03), consistent with the interpretation that limiting contrast exposure and procedural duration in a shocked patient protects the kidney. A mediation analysis of the MATRIX trial provided the mechanistic counterpart in the access-site domain: multistate modelling demonstrated that the transition from acute kidney injury to death was substantially less likely after radial access (hazard ratio 0.55, 0.31 to 0.97), and that the pathway from coronary intervention through acute kidney injury to death carried a hazard ratio of 0.49 (0.26 to 0.92), whereas the pathway mediated by bleeding showed no such effect (hazard ratio 1.05, 0.42 to 2.64). The prevention of acute kidney injury, rather than the prevention of bleeding, therefore appears to account for the greater part of the mortality benefit attributed to radial access.^{18,26}

Table 16. Acute kidney injury, contrast nephropathy and renal-replacement therapy

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Thiele et al. (2017)	Culprit-only vs immediate multivessel PCI in shock	Renal-replacement therapy	Reference	RR 0.71 (0.49–1.03)	0.07
Thiele et al. (2017)	Culprit-only vs immediate multivessel PCI in shock	Death or renal-replacement therapy 45.9%	55.4%	RR 0.83 (0.71–0.96)	0.01
Rothenbühler et al. (2019)	Radial vs femoral access (MATRIX)	Transition from acute kidney injury to death	Reference	HR 0.55 (0.31–0.97)	< 0.05
Rothenbühler et al. (2019)	Radial vs femoral access (MATRIX)	Pathway PCI → acute kidney injury → death	Reference	HR 0.49 (0.26–0.92)	< 0.05
Kim et al. (2025)	Immediate vs staged complete revascularisation	Contrast-induced nephropathy	Reference	No significant difference	Not significant
Bernat et al. (2014)	Radial vs femoral access	Contrast volume 170 ± 71 mL	182 ± 60 mL	Mean difference –12 mL	0.01
Gershlick et al. (2015)	Complete vs infarct-related-artery-only PCI	Contrast-induced nephropathy	Reference	No significant difference in safety endpoints	Not significant
Landi et al. (2025)	Mayo Clinic risk score in MATRIX	Contrast-associated acute kidney injury	Reference	ROC-AUC 0.70 (0.67–0.72)	Model discrimination

Reperfusion success and procedural performance

Eight studies reported measures of reperfusion success. The clearest demonstration that angiographic patency is not a valid surrogate for clinical benefit comes from LIPSIA-STEMI, in which pre-procedural Thrombolysis in Myocardial Infarction grade 2 or 3 flow was achieved in 71 per cent of patients receiving pre-hospital tenecteplase-facilitated PCI compared with 35 per cent undergoing primary PCI ($p < 0.001$), yet infarct size measured by delayed-enhancement magnetic resonance imaging was numerically larger in the facilitated arm (17.9 per cent of the left ventricle versus 13.7 per cent; $p = 0.10$), with strong trends towards more early and late microvascular obstruction. The same dissociation was demonstrated on a larger scale for thrombus aspiration, which improved ST-segment resolution and reduced angiographic distal embolisation in TOTAL without any corresponding clinical benefit; the reduction in distal embolisation was greatest in patients with the shortest ischaemic times (odds ratio 0.23, 0.09 to 0.62 below two hours) and absent beyond six hours, yet no clinical benefit emerged in any time stratum.^{7,29,82}

Table 18. Reperfusion success, infarct size and procedural performance

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Thiele et al. (2011)	Facilitated vs primary PCI	Pre-procedural TIMI 2–3 flow 71%	35%	Absolute difference +36%	< 0.001
Thiele et al. (2011)	Facilitated vs primary PCI	Infarct size 17.9% of left ventricle	13.7%	Larger with facilitated PCI	0.10
Jolly et al. (2016)	Thrombectomy vs PCI alone	Improved ST-segment resolution and reduced distal embolisation	Reference	Surrogate benefit without clinical benefit	Reported
Moxham et al. (2021)	Thrombectomy stratified by ischaemic time	Distal embolisation OR 0.23 (0.09–0.62) if < 2 h	OR 0.70 (0.33–1.50) if > 6 h	Interaction across ischaemic time	0.12

Sabaté et al. (2012/2016)	Everolimus-eluting vs bare-metal stent	Procedural success 97.5%	94.6%	Absolute difference +2.9%	0.0050
Keeley et al. (2006)	Facilitated vs primary PCI (pooled trial data)	Initial TIMI 3 flow 37%	15%	OR 3.18 (2.22–4.55); final TIMI 3 flow not different	< 0.001
Şahin et al. (2026)	Admission EASIX and no-reflow	No-reflow 14.1% of the cohort	Reference	Adjusted OR 1.485 (1.286– 1.715); ROC- AUC 0.706	< 0.001
Barthélémy et al. (2021)	Residual SYNTAX score in cardiogenic shock	Complete revascularisation achieved in 25.2% of multivessel PCI	9.3% of culprit-only PCI	Adjusted OR 1.49 (1.11– 2.01) per 10 units for 30- day death	< 0.05

Prognostic discrimination and the effect of reperfusion delay

Twelve studies contributed to this domain, which has two components. The first is the relationship between delay and death. In the Western Denmark cohort of 6 209 consecutive patients, long-term mortality rose monotonically across strata of system delay, from 15.4 per cent when the delay was sixty minutes or less to 23.3 per cent at 61 to 120 minutes, 28.1 per cent at 121 to 180 minutes and 30.8 per cent at 181 to 360 minutes ($p < 0.001$), with an adjusted hazard ratio of 1.10 (1.04 to 1.16) for each additional hour. In the National Cardiovascular Data Registry, adjusted in-hospital mortality rose continuously and non-linearly with door-to-balloon time, from 3.0 per cent at thirty minutes through 4.3 per cent at ninety minutes to 8.4 per cent at one hundred and eighty minutes; reducing door-to-balloon time from ninety to sixty minutes was associated with 0.8 per cent lower mortality and from sixty to thirty minutes with a further 0.5 per cent. In a Korean multicentre registry of 5 243 patients, each hour of door-to-balloon delay carried an adjusted hazard ratio of 1.90 (1.51 to 2.39) for one-year death, and reduction below forty-five minutes conferred additional benefit relative to ninety minutes (adjusted hazard ratio 0.30, 0.19 to 0.42), demonstrating that no plateau of benefit has yet been identified.^{35,36,38}

The second component is prognostic discrimination. Eleven models were identified whose areas under the receiver-operating-characteristic curve ranged from 0.709 for the Thrombolysis in Myocardial Infarction risk score applied to elderly women in a developing-country cohort, through 0.780 for the original Global Registry of Acute Coronary Events score, 0.810 for the admission Endothelial Activation and Stress Index, 0.821 for the CADILLAC score in diabetic patients and 0.878 for a modified GRACE score incorporating continuous high-sensitivity troponin T, to 0.947 for a ten-variable nomogram developed in thirty-nine Chinese hospitals and 0.959 for the RURUS SURYAWAN score validated in an Indonesian cohort of 1 535 patients. A machine-learning model developed in a multi-ethnic Malaysian registry outperformed the TIMI score at every time horizon (0.88 versus 0.81 in hospital, 0.90 versus 0.80 at thirty days and 0.84 versus 0.76 at one year; $p < 0.0001$ for each comparison) and correctly classified ninety per cent of non-survivors as high risk compared with only ten to thirty per cent classified as such by TIMI. The reconstructed curves are displayed in Figure 8 and the corresponding areas under the curve in Figure 9.^{44,46,47,48,49,50,51}

Table 19. prognostic discrimination and the effect of reperfusion delay

Study (year)	Model or exposure	Population / setting	Endpoint	Discrimination (AUC or C-index)	p value
Wang et al. (2022)	Ten-variable clinical nomogram	855 STEMI patients, 39 Chinese hospitals	In-hospital death	0.947 (0.927–0.967) derivation; 0.891 (0.844–0.939) validation	< 0.001
Gde et al. (2025)	RURUS SURYAWAN score	1 535 first acute MI patients undergoing primary PCI, Indonesia	30-day death	0.944 (0.906–0.972) derivation; 0.959 (0.921–0.983) validation	< 0.001

Aziz et al. (2021)	Machine-learning model vs TIMI score	6 299 Asian STEMI patients	In-hospital, 30-day and 1-year death	0.88 / 0.90 / 0.84 vs TIMI 0.81 / 0.80 / 0.76	< 0.0001
Georgiopoulos et al. (2023)	Modified GRACE with continuous hs-cTnT	9 450 patients with acute coronary syndrome	In-hospital death	0.878 vs 0.780 for the original GRACE score	Net reclassification 0.097
Kao et al. (2020)	CADILLAC vs TIMI, GRACE and PAMI	455 Taiwanese diabetic STEMI patients	6-, 12- and 24-month death	CADILLAC 0.821, 0.821 and 0.819; all scores 0.67–0.82	< 0.0001
Littnerová et al. (2015)	Six risk scores compared head-to-head	593 STEMI patients treated with primary PCI	6- and 12-month death; heart-failure admission	0.73–0.85 for mortality; Zwolle 0.80–0.83 for heart failure	< 0.05
Şahin et al. (2026)	Admission EASIX	1 931 STEMI patients	In-hospital death; no-reflow	0.810 and 0.706	< 0.001
Furnaz et al. (2019)	TIMI risk score	404 elderly women undergoing primary PCI	In-hospital and post-discharge death	0.709 (0.591–0.827) and 0.689 (0.608–0.770)	< 0.001
Goriki et al. (2020)	Five-variable laboratory score	1 027 STEMI patients	In-hospital death	0.853 derivation; 0.879 validation; no difference vs GRACE	0.721 vs GRACE
Landi et al. (2025)	Mayo Clinic PCI risk score	6 724 patients with acute	In-hospital death	0.88 (0.85–0.91) for model	Well calibrated

	(MATRIX validation)	coronary syndrome		A and 0.88 (0.84–0.92) for model B	
Terkelsen et al. (2010)	System delay as a continuous exposure	6 209 primary PCI patients	Long-term death	Adjusted HR 1.10 (1.04–1.16) per additional hour	< 0.001
Park et al. (2019)	Door-to-balloon time as a continuous exposure	5 243 primary PCI patients	1-year death	Adjusted HR 1.90 (1.51–2.39) per hour of delay	< 0.001

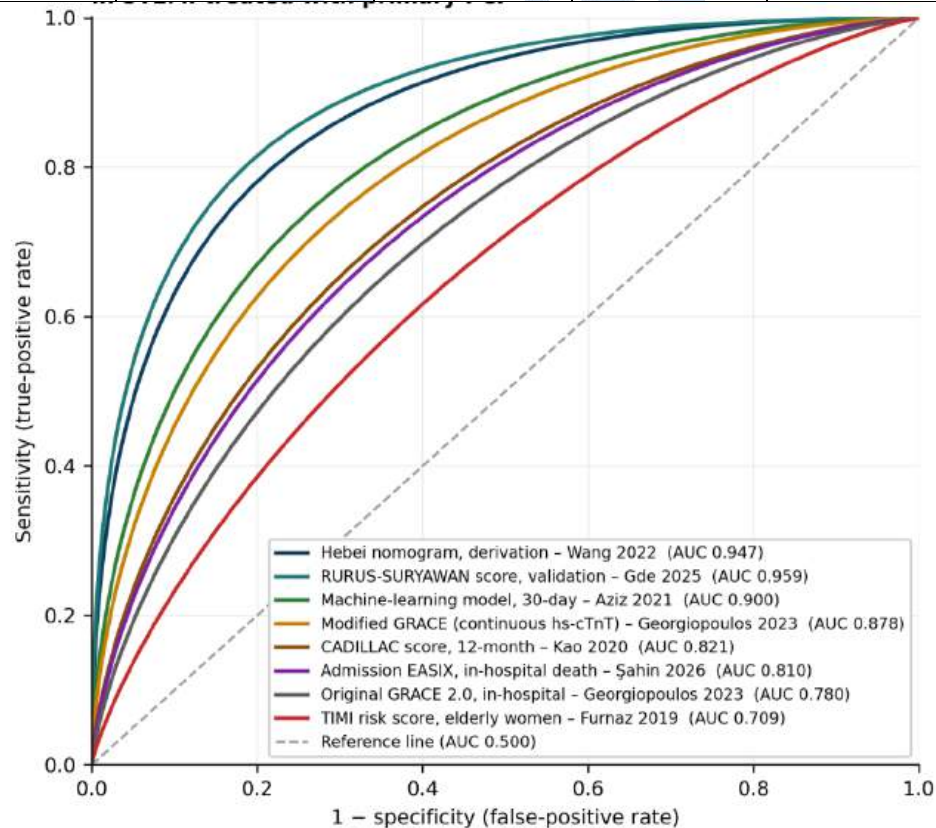


Figure 8. Receiver-operating-characteristic curves for eight prognostic models applied to patients with STEMI treated by primary PCI. Curves were reconstructed from the areas under the curve reported by each source study using a binormal model with equal variances; they represent the

reported discriminative performance rather than the raw sensitivity–specificity pairs of the original analyses.

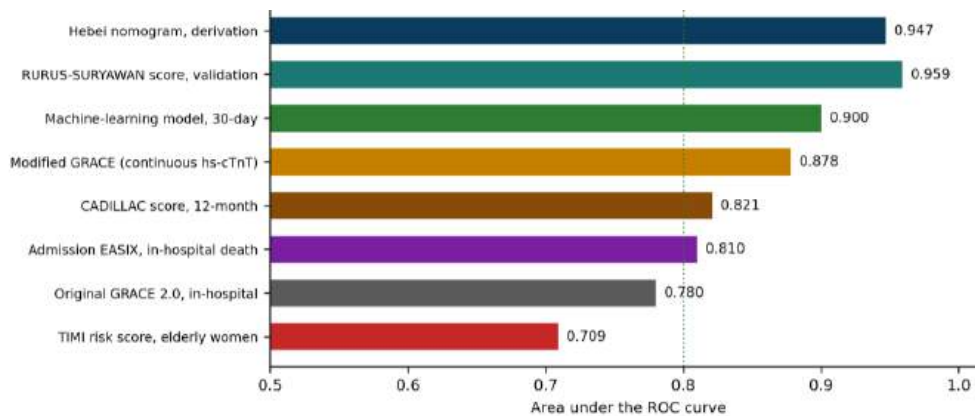


Figure 9. Areas under the receiver-operating-characteristic curve reported by the included prognostic studies. The dotted line at 0.80 marks the conventional threshold for good discrimination.

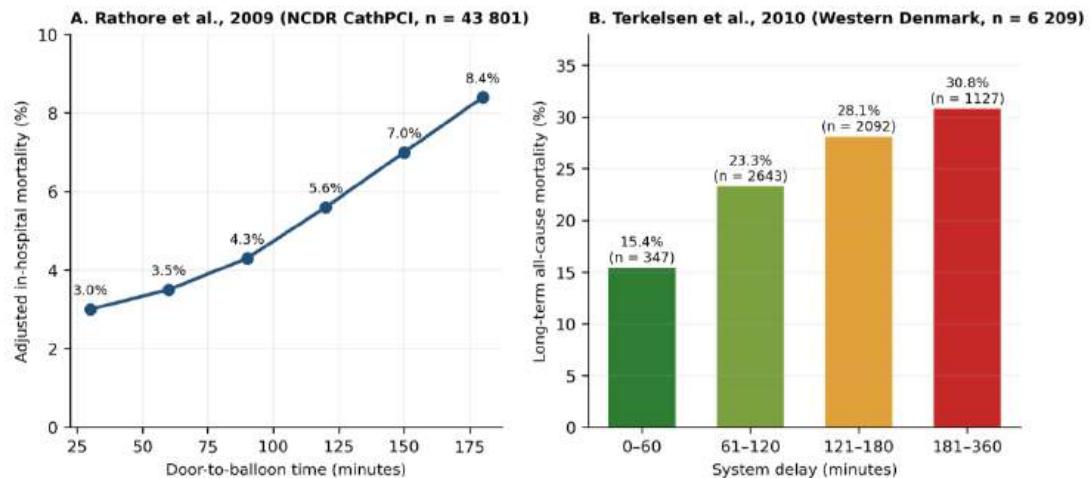


Figure 10. Dose–response relationship between reperfusion delay and mortality. Panel A shows adjusted in-hospital mortality as a function of door-to-balloon time in 43 801 patients; panel B shows long-term all-cause mortality by system-delay stratum in 6 209 patients.

Health status and resource utilisation

Patient-reported outcomes were reported by one large randomised trial and resource use by three. In the pre-specified health-status analysis of COMPLETE, the Seattle Angina Questionnaire angina-frequency score rose from a mean of 87.1 at baseline to 97.1 at a median of three years in

the complete-revascularisation group and from 87.2 to 96.3 in the culprit-lesion-only group, a between-group difference of 0.97 points (0.27 to 1.67; $p = 0.006$). The proportion entirely free of angina was 87.5 per cent and 84.3 per cent respectively, an absolute difference of 3.2 percentage points (0.7 to 5.7; $p = 0.01$), and this benefit was concentrated in patients whose non-culprit stenosis was eighty per cent or greater (absolute difference 4.7 per cent; p for interaction 0.02). The magnitude of this effect is modest and falls below the threshold usually regarded as clinically important for an individual patient, which is an honest and important qualification: the case for complete revascularisation rests principally on the prevention of events, not on symptom relief. Radial access shortened hospital stay by a median of one day in RIFLE-STEACS ($p = 0.03$) and intensive-care stay by 0.5 days in STEMI-RADIAL ($p = 0.0038$).^{10,20,21}

Table 20. health status, angina burden and resource utilisation

Study (year)	Comparison	Intervention arm	Comparator arm	Effect estimate (95% CI)	p value
Mehta et al. (2022)	Complete vs culprit-only revascularisation	SAQ angina-frequency score 97.1 ± 9.7	96.3 ± 10.9	Between-group difference 0.97 points (0.27–1.67)	0.006
Mehta et al. (2022)	Complete vs culprit-only revascularisation	Angina-free 1457 (87.5%)	1376 (84.3%)	Absolute difference 3.2% (0.7–5.7)	0.01
Mehta et al. (2022)	Non-culprit stenosis $\geq 80\%$ subgroup	Angina-free proportion	Reference	Absolute difference 4.7%	Interaction 0.02
Romagnoli et al. (2012)	Radial vs femoral access	Hospital stay 5 days (IQR 4–7)	6 days (IQR 5–8)	Median difference –1 day	0.03
Bernat et al. (2014)	Radial vs femoral access	Intensive-care stay 2.5 ± 1.7 days	3.0 ± 2.9 days	Mean difference –0.5 days	0.0038

Bueno et al. (2010)	Primary PCI vs fibrinolysis, elderly	Recurrent ischaemia 0.8%	9.7%	Absolute difference –8.9%	< 0.001
Sabaté et al. (2016)	Everolimus-eluting vs bare-metal stent	Patient-oriented composite	Reference	HR 0.80 (0.65–0.98) reflecting fewer repeat procedures	0.033

Quantitative synthesis, heterogeneity and sensitivity analyses

Three comparisons satisfied the pre-specified conditions for pooling. In the reperfusion comparison, the two randomised trials of primary PCI against stand-alone fibrinolysis pooled to 0.85 (0.75 to 0.96) with no heterogeneity, whereas the two randomised trials of primary PCI against a pharmacoinvasive strategy pooled to 1.20 (0.98 to 1.48; $p = 0.077$), also without heterogeneity — a striking demonstration that the apparent inconsistency of the reperfusion literature dissolves once the comparator is correctly specified. In the complete-revascularisation comparison, the four eligible trials pooled to a hazard ratio of 0.71 (0.54 to 0.91; $p = 0.008$) with moderate heterogeneity ($I^2 = 63$ per cent, $\tau^2 = 0.040$); the angiography-guided subgroup yielded 0.63 (0.40 to 0.99) and the physiology-guided subgroup 0.74 (0.45 to 1.21), the confidence intervals overlapping widely so that the review cannot demonstrate a genuine difference between lesion-selection strategies. In the access-site comparison, the six eligible estimates pooled to 0.64 (0.46 to 0.90; $p = 0.010$) with moderate heterogeneity ($I^2 = 57$ per cent).^{8,12,13,14,20,21,22,25}

Sensitivity analyses are set out in Table 22. The pooled benefit of complete revascularisation was preserved under a fixed-effect model (0.76, 0.67 to 0.86) and under leave-one-out re-estimation, but attenuated towards the null when the analysis was restricted to the two largest contemporary trials with fully adjudicated hard endpoints (0.82, 0.66 to 1.03). The mortality advantage of radial access proved less robust: excluding RIFLE-STEACS, the single trial judged to be at high risk of bias, moved the estimate to 0.70 (0.47 to 1.05) and abolished statistical significance, indicating that this conclusion should be regarded as provisional. The funnel plot in Figure 11 shows no gross asymmetry, but with a maximum of six studies per comparison it cannot exclude small-study effects and no formal test of asymmetry was performed.

Table 21. Summary of pooled random-effects analyses

Comparison / subgroup	Studies (k)	Participants	Pooled estimate (95% CI)	I ²	τ ²	Z	p
Primary PCI vs stand-alone fibrinolysis (randomised)	2	1 838	0.85 (0.75–0.96)	0%	0.000	2.53	0.011
Primary PCI vs pharmacoinvasive strategy (randomised)	2	2 732	1.20 (0.98–1.48)	0%	0.000	1.77	0.077
Primary PCI vs on-site fibrinolysis (observational)	1	19 334	0.38 (0.32–0.44)	—	—	12.29	< 0.001
Complete vs culprit-only revascularisation — overall	4	6 506	0.71 (0.54–0.91)	63%	0.040	2.64	0.008
Angiography-guided subgroup	2	4 337	0.63 (0.40–0.99)	54%	0.067	1.98	0.047
FFR-guided subgroup	2	2 169	0.74 (0.45–1.21)	79%	0.102	1.19	0.234
Transradial vs transfemoral access — overall	6	10 675	0.64 (0.46–0.90)	57%	0.093	2.57	0.010
Mortality subgroup	4	5 958	0.64 (0.41–0.98)	40%	0.078	2.05	0.041
Net adverse clinical events subgroup	2	4 717	0.61 (0.29–1.29)	82%	0.242	1.29	0.198

Effect estimates are hazard ratios, odds ratios or relative risks as reported by the contributing studies and are combined on the logarithmic scale. Values below 1.0 favour the first-named strategy.

Table 22. Sensitivity and robustness analyses

Analysis	Rationale	Result	Interpretation
Leave-one-out, complete revascularisation	Assess dominance of the largest trial	Omitting COMPLETE: HR 0.66 (0.44–0.99); omitting FULL REVASC: HR 0.62 (0.47–0.81)	The pooled benefit is not driven by any single trial, although precision falls

			when COMPLETE is removed
Fixed-effect re-analysis, complete revascularisation	Test the influence of the between-study variance component	HR 0.76 (0.67–0.86), $p < 0.001$	Direction and significance are preserved under a fixed-effect model
Restriction to trials with adjudicated hard endpoints	Reduce outcome-ascertainment bias	COMPLETE and FULL REVASC only: HR 0.82 (0.66–1.03)	Effect attenuates towards the null when only the two largest contemporary trials are used
Exclusion of trials at high or unclear risk of bias, radial access	Test robustness to risk-of-bias judgements	Excluding RIFLE-STEACS: OR 0.70 (0.47–1.05)	Statistical significance is lost, indicating that the mortality signal is sensitive to the inclusion of one open-label trial
Exclusion of the observational stratum, reperfusion analysis	Avoid confounding by indication	Randomised subgroup A alone: 0.85 (0.75–0.96)	The randomised evidence alone supports a modest but significant advantage for primary PCI
Alternative effect measure (risk ratio instead of odds ratio)	Test measure dependency where event rates exceed 10%	Radial versus femoral: RR 0.66 (0.48–0.91)	Conclusions are stable across effect measures

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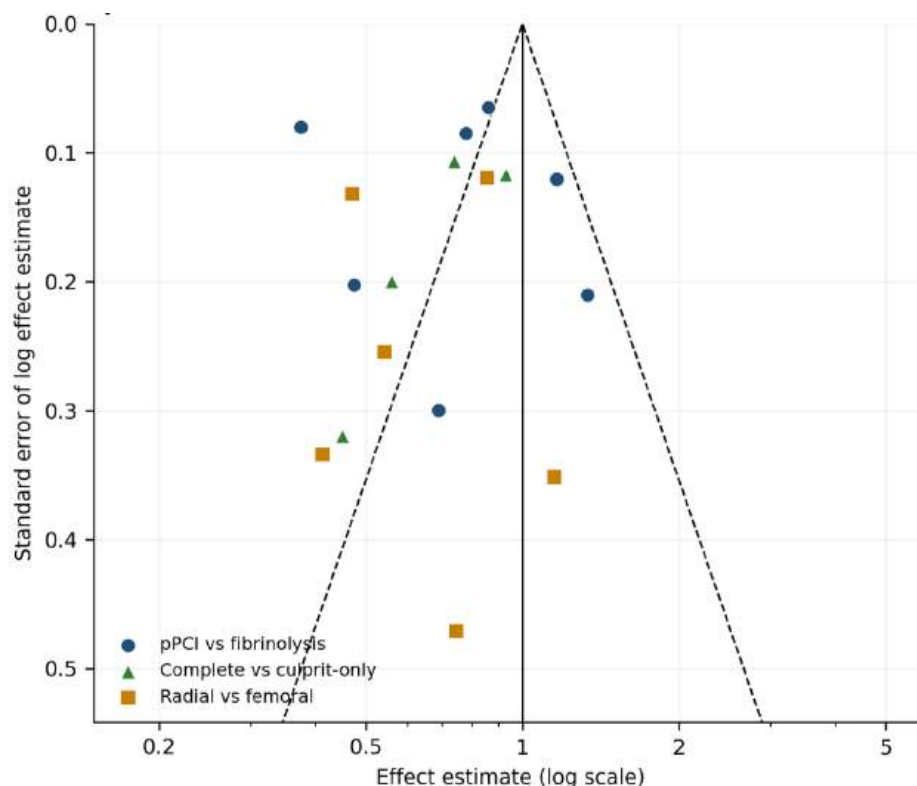


Figure 11. Contour-free funnel plot of all effect estimates contributing to the three pooled comparisons, with pseudo-95% confidence limits. Formal tests of asymmetry were not performed because no comparison included ten or more studies.

Certainty of the evidence

The GRADE assessment is presented in Table 23. Certainty was rated high for five outcomes: long-term mortality and re-infarction after primary PCI relative to fibrinolysis, repeat revascularisation after complete revascularisation, major bleeding after radial access, mortality after routine thrombus aspiration, and the device-oriented composite after drug-eluting stent implantation. Certainty was moderate for short-term mortality after primary PCI (downgraded for imprecision and for the age of the randomised evidence), for cardiovascular death or myocardial infarction after complete revascularisation (downgraded for inconsistency), for stroke after thrombus aspiration (downgraded for imprecision) and for the culprit-only strategy in cardiogenic shock (downgraded because a single trial supplies the entire evidence base). Certainty was low for all-cause mortality after radial access, for the relationship between reperfusion delay and mortality,

and for the prognostic-model literature, the last principally because most models have never been externally validated in a population other than that in which they were derived.

Table 23. GRADE summary of findings

Outcome	Studies	Participants	Effect	Certainty (GRADE)	Reasons for downgrading
Short-term mortality, primary PCI vs fibrinolysis	2 RCTs + 1 large cohort	21 172	0.85 (0.75–0.96) randomised	⊕⊕⊕○ Moderate	Imprecision; most randomised evidence predates contemporary antithrombotic therapy
Long-term mortality and re-infarction, primary PCI vs fibrinolysis	2 RCT reports	1 572	HR 0.86 (0.76–0.98) for death or re-MI at 16 y	⊕⊕⊕⊕ High	Not downgraded; near-complete registry-based follow-up
Cardiovascular death or MI, complete vs culprit-only	4 RCTs	6 506	HR 0.71 (0.54–0.91)	⊕⊕⊕○ Moderate	Inconsistency ($I^2 = 63\%$) attributable to lesion-selection strategy
Repeat revascularisation, complete vs culprit-only	3 RCTs	4 964	HR 0.45–0.56 across trials	⊕⊕⊕⊕ High	Large, consistent effect across trials
All-cause mortality, radial vs femoral access	4 RCTs	5 958	OR 0.64 (0.41–0.98)	⊕⊕○○ Low	Inconsistency and risk of bias from open-label design; SAFARI-STEMI stopped early
Major bleeding and access-site complications, radial vs femoral	3 RCTs	4 000	Absolute reductions of 4.4–5.8 percentage points	⊕⊕⊕⊕ High	Consistent, large and clinically important effect

Mortality, routine thrombus aspiration vs PCI alone	3 RCT reports	17 976	HR 0.94–1.00	⊕⊕⊕⊕ High	Two very large trials with registry-complete follow-up
Stroke, routine thrombus aspiration vs PCI alone	2 RCT reports	10 732	HR 1.66 (1.10–2.51) at 1 y	⊕⊕⊕○ Moderate	Imprecision; low absolute event numbers
Device-oriented composite, drug-eluting vs bare-metal stents	2 RCT reports	1 498	HR 0.72 (0.55–0.93) at 10 y	⊕⊕⊕⊕ High	Complete 10-year follow-up in 95% of patients
Culprit-only vs immediate multivessel PCI in cardiogenic shock	1 RCT (2 reports)	706	RR 0.83 (0.71–0.96) at 30 d	⊕⊕⊕○ Moderate	Single trial; attenuation of the effect at 1 year
Reperfusion delay and mortality	6 cohorts	221 435	Adjusted HR 1.10–1.90 per hour of delay	⊕⊕○○ Low	Observational design with residual confounding, offset by a consistent dose–response gradient
Prognostic discrimination of risk models	10 cohorts	≈ 30 000	AUC 0.71–0.96	⊕⊕○○ Low	Heterogeneous models, frequent absence of external validation, risk of overfitting

DISCUSSION

Principal findings

This systematic review of thirty-three primary studies enrolling more than 320 000 patients supports four principal conclusions. First, primary percutaneous coronary intervention is superior to stand-alone fibrinolysis for death-containing composite endpoints, with a pooled estimate of 0.85 (0.75 to 0.96) in randomised trials and no detectable heterogeneity, and this advantage is durable to sixteen years, being driven by the prevention of re-infarction and of cardiac death rather than by an early reduction in all-cause mortality. Second, that advantage is strictly conditional on

time: it is amplified more than twofold when the PCI-related delay is under sixty minutes and is entirely abolished once that delay approaches two hours, at which point a pharmacoinvasive strategy becomes an equivalent alternative. Third, three adjuncts to primary PCI improve outcomes — complete revascularisation of significant non-culprit lesions, transradial arterial access and new-generation drug-eluting stents — while two widely adopted practices do not: routine manual thrombus aspiration confers no benefit and causes stroke, and immediate multivessel intervention in cardiogenic shock increases death and renal failure. Fourth, prognostic discrimination in this population is achievable with areas under the receiver-operating-characteristic curve above 0.90, but the models that achieve this have rarely been validated outside their derivation cohorts.^{1,8,20,29,43}

Reperfusion strategy: the comparator determines the answer

The most methodologically consequential finding of this review is that the apparent inconsistency of the reperfusion literature is an artefact of comparator misspecification. When primary PCI is compared with fibrinolysis administered without a planned subsequent angiographic strategy, it is superior; when it is compared with pre-hospital fibrinolysis followed by routine angiography within six to twenty-four hours — the pharmacoinvasive strategy — it is not. Each of these two subgroups was internally homogeneous in the present analysis ($I^2 = 0$ per cent in both), yet pooling them together produced an I^2 of 96 per cent and a non-significant summary estimate. The distinction is not merely statistical: it corresponds to two entirely different clinical questions, and conflating them has been a persistent source of confusion in the interpretation of trials such as STREAM and CAPTIM.^{4,5,6}

The clinical implication is that the choice of reperfusion strategy should be governed by the achievable PCI-related delay rather than by an abstract preference for mechanical over pharmacological reperfusion. The Chinese National Chest Pain Center Program data place the equipoise threshold at 119.5 minutes of PCI-related delay in the population as a whole, with lower thresholds among older patients, those with anterior infarction and those in higher Killip classes — that is, precisely the patients in whom the absolute risk is greatest and the tolerance for delay least. This finding is consonant with the PCAT-2 collaboration, which analysed individual data from 6 763 patients randomised in twenty-two trials and demonstrated that although the relative mortality reduction with primary PCI was constant across the risk spectrum, the number needed to treat to prevent one death fell from 516 in the lowest risk quartile to seventeen in the highest. A

network meta-analysis of thirty-one contemporary trials reached a compatible conclusion, ranking primary PCI first for mortality (odds ratio 0.73, 0.61 to 0.89 against fibrinolysis) and the pharmacoinvasive approach second (0.79, 0.59 to 1.08), while facilitated PCI performed worst.^{43,55,65}

For Indonesian practice this is more than an academic distinction. Across an archipelago of more than seventeen thousand islands, in which catheterisation laboratories are concentrated in the largest cities of Java, Sumatra and Sulawesi, a PCI-related delay of under two hours is unattainable for a substantial proportion of the population. The evidence assembled here indicates that in such settings the correct response is not to transport patients for prolonged periods to a distant catheterisation laboratory, but to establish pre-hospital or district-hospital fibrinolysis followed by transfer for angiography within six to twenty-four hours — a strategy shown by meta-analysis of seven trials in 2 961 patients to reduce re-infarction (odds ratio 0.55, 0.36 to 0.82) and recurrent ischaemia (0.25, 0.13 to 0.49) relative to ischaemia-guided management, without excess major bleeding.^{43,65,67}

Time as the dominant effect modifier

Six cohorts contributed to a remarkably consistent picture of the delay–mortality relationship. The gradient is monotonic, it is present across every measure of delay examined, and it shows no evidence of a plateau even at door-to-balloon times below sixty minutes. Two subtleties deserve emphasis. The first is that the population-level and individual-level relationships can diverge: in the National Cardiovascular Data Registry, median door-to-balloon time fell from eighty-six to sixty-three minutes between 2005 and 2011 while risk-adjusted in-hospital mortality rose from 4.7 to 5.3 per cent, yet within individuals each ten-minute reduction remained associated with an adjusted odds ratio of 0.92 for in-hospital death. The explanation is that the population undergoing primary PCI changed over the period, coming to include progressively sicker patients; the absence of a population-level signal must not be misread as evidence that individual delay does not matter.³⁷

The second subtlety is that door-to-balloon time is the wrong metric in isolation. In CREDO-Kyoto, a door-to-balloon time under ninety minutes was associated with improved outcome only among patients presenting within two hours of symptom onset (adjusted hazard ratio 0.58, 0.38 to 0.87), and was actually associated with worse outcome among late presenters (1.57,

1.12 to 2.18), with a significant interaction ($p = 0.01$). Total ischaemic time — and therefore patient-related delay, which in the Victorian registry was fourfold larger than the sex difference in door-to-balloon time — is the variable that determines myocardial salvage. Public-awareness campaigns and emergency-medical-service field triage, which reduced the composite of death or non-fatal infarction by a third in a Danish cohort (hazard ratio 0.67, 0.46 to 0.97), address the larger part of the problem than any further compression of in-hospital process time.^{38,40,78}

Completeness of revascularisation and the FULL REVASC discrepancy

The pooled hazard ratio of 0.71 (0.54 to 0.91) for complete versus culprit-lesion-only revascularisation conceals a genuine and unresolved tension. Three trials — COMPLETE, DANAMI-3-PRIMULTI and CvLPRIT — demonstrated benefit, whereas FULL REVASC, which randomised 1 542 patients and followed them for a median of 4.8 years, found none (hazard ratio 0.93, 0.74 to 1.17). Three explanations merit consideration. The first is the method of lesion selection: FULL REVASC and DANAMI-3-PRIMULTI both used fractional flow reserve, yet these two trials produced the most discordant results of the four, which argues against lesion-selection method as the sole explanation, and the subgroup analysis in the present review found overlapping confidence intervals between angiography-guided and physiology-guided strategies. The second is the duration of follow-up: the benefit of complete revascularisation in COMPLETE emerged mainly after forty-five days (hazard ratio 0.69, 0.54 to 0.89 beyond that landmark, compared with 0.86, 0.59 to 1.24 before it), and FULL REVASC, with the longest follow-up, might have been expected to show more rather than less benefit — so this too is an incomplete explanation. The third, and in the judgement of the present authors the most plausible, is the completeness actually achieved: a core-laboratory analysis of COMPLETE demonstrated that patients in whom a residual SYNTAX score of zero was achieved experienced a hazard ratio of 0.61 (0.48 to 0.77) for cardiovascular death or myocardial infarction, whereas those in whom complete revascularisation was intended but not achieved experienced no benefit whatever (0.98, 0.61 to 1.57), with a highly significant interaction ($p < 0.001$).^{8,12,13,14}

Contemporaneous meta-analyses are consistent with the pooled estimate reported here. A synthesis of ten randomised trials in 7 030 patients found complete revascularisation to reduce cardiovascular death (odds ratio 0.69, 0.48 to 0.99) with no heterogeneity between fractional-flow-reserve-guided and angiography-guided strategies (p for interaction 0.52), and a further synthesis

of six trials in 6 528 patients found a hazard ratio of 0.62 (0.39 to 0.97) for cardiovascular death, with a number needed to treat of seventy for cardiovascular death, forty-five for myocardial infarction and eight for repeat revascularisation. A network meta-analysis of twenty-six trials in 15 902 patients found both immediate and staged complete revascularisation superior to culprit-vessel-only treatment, and immediate complete revascularisation superior to staged (relative risk 0.74, 0.56 to 0.97), although that advantage was substantially diminished after periprocedural infarction was excluded from the definition of myocardial infarction.^{56,57,58,59}

The practical synthesis is therefore that non-culprit lesions should be treated, that the intention to treat them is insufficient and that anatomical completeness is what confers benefit, and that the timing should be early — during the index admission — rather than deferred by weeks. Whether the non-culprit intervention should be performed during the index procedure or on a subsequent day of the same admission remains genuinely uncertain, MULTISTARS AMI favouring the former and OPTION-STEMI failing to demonstrate non-inferiority of the former, with a numerical excess of in-hospital cardiogenic shock in the immediate arm that warrants caution in haemodynamically marginal patients.^{15,16,59}

Arterial access: mechanism, magnitude and the limits of the evidence

Transradial access reduces access-site bleeding and vascular complications by a margin that is large, consistent and not seriously disputed. Whether it reduces mortality is a more delicate question, and the present review's sensitivity analysis — in which excluding a single high-risk-of-bias trial abolished statistical significance — counsels humility. Nonetheless, the direction of effect is consistent across an individual-patient-data meta-analysis of 21 600 patients from seven trials (hazard ratio 0.77, 0.63 to 0.95 for all-cause mortality; odds ratio 0.55, 0.45 to 0.67 for major bleeding), a trial sequential analysis of seventeen studies in 19 328 patients that crossed the monitoring boundary for mortality, and a further trial sequential analysis confined to 11 992 STEMI patients that reported firm evidence of benefit for thirty-day mortality (relative risk 0.72, 0.58 to 0.90), major bleeding, major adverse cardiovascular events and access-site complications.^{60,62,63}

The mechanistic evidence is unexpected and clinically instructive. Multistate mediation analysis of the MATRIX trial demonstrated that the mortality benefit of radial access was mediated predominantly through the prevention of acute kidney injury rather than through the prevention of

bleeding, and the individual-patient-data meta-analysis found that the mortality advantage was concentrated in patients with moderate or severe baseline anaemia (p for interaction 0.003) and that bleeding prevention only partially explained the causal association. If this is correct, then the benefit of radial access is not simply a haemostatic phenomenon and cannot be fully substituted by vascular closure devices or by bivalirudin — which may in turn explain the neutral result of SAFARI-STEMI, a trial in which nearly ninety per cent of patients received bivalirudin and more than two thirds of femoral procedures used a closure device.^{22,26,60}

Thrombus aspiration: a cautionary tale about surrogate endpoints

The trajectory of manual thrombus aspiration from guideline-endorsed routine practice to a class III recommendation is the clearest illustration in contemporary interventional cardiology of the danger of adopting a therapy on the strength of surrogate endpoints. Aspiration reliably improves ST-segment resolution and reduces angiographic distal embolisation, and a single-centre trial reported a near-halving of one-year mortality. Two subsequent large trials, enrolling 7 244 and 10 732 patients respectively, found no clinical benefit; the larger of the two found a significant excess of stroke at one year (hazard ratio 1.66, 1.10 to 2.51). An individual-patient meta-analysis of all three trials in 18 306 patients confirmed the absence of benefit for cardiovascular death at thirty days (hazard ratio 0.84, 0.70 to 1.01) and a borderline excess of stroke or transient ischaemic attack (odds ratio 1.43, 0.98 to 2.10); within the high-thrombus-burden subgroup, cardiovascular death was lower (0.80, 0.65 to 0.98) but stroke was higher (1.56, 1.02 to 2.42), with non-significant interaction terms for both, so that the subgroup finding must be regarded as hypothesis-generating rather than practice-changing.^{27,29,30,64,82}

Two nuances qualify this conclusion. Registry data from Sweden suggest that aspiration reduces stent thrombosis (risk reduction –2.7 per cent at thirty days), and an analysis of the Osaka Acute Coronary Insufficiency Study found that the apparent excess of periprocedural stroke was heavily institution-dependent, disappearing once hospital was modelled as a random effect (odds ratio 0.91, 0.71 to 1.16) with significant heterogeneity between institutions (p for interaction 0.007). The reasonable interpretation is that routine aspiration should be abandoned, that selective bail-out aspiration in the presence of a very large thrombus burden remains defensible, and that operator technique and institutional protocol materially modify the stroke hazard.⁸³

Cardiogenic shock: where less intervention is more

Cardiogenic shock complicates up to ten per cent of acute myocardial infarctions and carries a thirty-day mortality approaching forty per cent and a one-year mortality approaching fifty per cent. CULPRIT-SHOCK demonstrated that in this population, and in contrast to the haemodynamically stable patient, restricting the index procedure to the culprit lesion reduced the composite of death or renal-replacement therapy at thirty days from 55.4 to 45.9 per cent (relative risk 0.83, 0.71 to 0.96), driven by an absolute 8.2 per cent reduction in death. The benefit attenuated by one year (relative risk 0.88, 0.76 to 1.01) and was purchased at the cost of a more than threefold increase in repeat revascularisation and a fourfold increase in heart-failure re-hospitalisation. The result was sufficiently robust to change European guidance to a class III recommendation against routine non-infarct-related artery revascularisation during primary PCI in shock, and was reproduced in a Polish national registry of 617 propensity-matched pairs (30-day death 49.3 versus 57.0 per cent).^{18,19,71}

This conclusion is not, however, uncontested, and the honest position is that it may not generalise to the most extreme end of the shock spectrum. In a pooled Korean analysis of 315 patients supported with veno-arterial extracorporeal membrane oxygenation before revascularisation, immediate multivessel PCI was associated with lower thirty-day death or renal-replacement therapy (54.3 versus 68.0 per cent) and lower twelve-month mortality (hazard ratio 0.689, 0.506 to 0.939), and a substudy of the DanGer Shock trial reported adjusted odds of death of 0.40 (0.19 to 0.83) with immediate multivessel PCI. Both analyses are observational and subject to confounding by indication in a direction that is difficult to predict, but they indicate that the CULPRIT-SHOCK result should not be extrapolated uncritically to patients already receiving mechanical circulatory support. The prognostic importance of achieving anatomical completeness is underlined by the observation that in CULPRIT-SHOCK the residual SYNTAX score was independently associated with thirty-day mortality (adjusted odds ratio 1.49 per ten units, 1.11 to 2.01) and with one-year mortality (1.52, 1.11 to 2.07).^{72,74,86}

Stent platform and the resolution of an old controversy

Concern that drug-eluting stents implanted into a thrombotic milieu would delay endothelialisation and provoke late stent thrombosis restricted their use in STEMI for a decade. The EXAMINATION programme has now resolved this question over ten years of follow-up: the patient-oriented composite occurred in 32.4 per cent of patients receiving an everolimus-eluting

stent and 38.0 per cent of those receiving a bare-metal stent (hazard ratio 0.81, 0.68 to 0.96), the device-oriented composite in 13.6 versus 18.4 per cent (0.72, 0.55 to 0.93), and definite stent thrombosis in 2.2 versus 2.5 per cent ($p = 0.590$), with only 0.6 and 0.4 per cent of events occurring between five and ten years. A trial-level network analysis spanning 34 068 patient-years found everolimus-eluting stents to reduce target-vessel revascularisation (relative risk 0.42 against bare-metal stents) and to have the lowest probability of stent thrombosis of any platform examined. Optical coherence tomographic imaging at five years nevertheless found more uncovered and malapposed struts with everolimus-eluting stents and more macrophage accumulation with bare-metal stents, a reminder that mechanistic and clinical endpoints need not align.^{31,32,69}

Whether ultrathin biodegradable-polymer platforms improve upon durable-polymer everolimus-eluting stents in STEMI is a more recent question. BIOSTEMI reported superiority for target-lesion failure at twelve months (relative risk 0.59, Bayesian credible interval 0.37 to 0.94) and at two years (0.58, 0.40 to 0.84), driven in both analyses by clinically indicated target-lesion revascularisation rather than by death or re-infarction. Interpretation is complicated by the Bayesian design, which incorporated historical priors from an earlier trial, by a fifteen per cent loss to follow-up, and by conduct in a single country with a low prevalence of complex lesions. In the broader coronary population, NORSTENT randomised 9 013 patients and found no difference between contemporary drug-eluting and bare-metal stents in the composite of death and spontaneous myocardial infarction at six years (16.6 versus 17.1 per cent), with repeat revascularisation the only endpoint favouring drug elution.^{33,34,85}

Prognostic models and the promise of risk-guided care

Eleven prognostic models were identified with discriminative performance ranging from adequate to excellent. Three observations follow. First, models incorporating continuous rather than dichotomised biomarker information perform materially better: the addition of continuous high-sensitivity troponin T to the GRACE score raised the area under the curve for in-hospital mortality from 0.780 to 0.878 with a continuous net reclassification improvement of 0.097. Second, models developed in one population frequently miscalibrate in another: the GRACE score discriminated equally well in white and ethnic-minority patients (area under the curve 0.87 in both) but systematically overestimated risk in ethnic minorities (expected-to-observed ratio 1.29), and GRACE 2.0 underestimated in-hospital mortality in women, prompting the development of a sex-

specific GRACE 3.0. Third, the very high areas under the curve reported by some recently derived scores — 0.947 for the Hebei nomogram and 0.959 for the RURUS SURYAWAN score validated in an Indonesian cohort — should be interpreted with the caution appropriate to models validated only by internal split-sample techniques within a single health system.^{44,50,51}

The clinical value of risk stratification lies less in prediction for its own sake than in identifying the patients for whom system delay must be compressed most aggressively. The FITT-STEMI observation that each ten minutes of contact-to-balloon delay costs 3.31 lives per hundred patients in cardiogenic shock but only 0.34 in stable patients means that a validated bedside identification of the highest-risk phenotype at first medical contact would permit rational prioritisation of catheterisation-laboratory activation, helicopter transfer and pre-hospital notification. That is a use of prognostic modelling for which the present evidence base is sufficient in principle but has not yet been operationalised in any published implementation trial.³⁹

Applicability to Indonesian and comparable health systems

None of the thirty-three included studies was conducted in Indonesia, and only one — the RURUS SURYAWAN score derived and validated in 1 535 patients at Dr Soetomo Hospital, Surabaya — was derived from an Indonesian population. This is the most important limitation of applicability in the present review. Several findings nevertheless translate directly. The equipoise threshold of approximately two hours of PCI-related delay, derived from a Chinese registry with a health-system structure closer to that of Indonesia than to that of Denmark or Canada, provides a defensible planning criterion for deciding where to build catheterisation capacity and where instead to invest in pre-hospital fibrinolysis and structured transfer. The observation that the mortality benefit of primary PCI over fibrinolysis was preserved in patients aged seventy-five and over, in whom the absolute risk is greatest, argues against age-based rationing of invasive care. The COVID-19 pandemic experience, in which a sixteen per cent reduction in primary PCI volume and a lengthening of total ischaemic time from 196 to 225 minutes were accompanied by an increase in thirty-day mortality from 6.5 to 8.0 per cent across 109 centres worldwide, is a natural experiment demonstrating what happens when a functioning STEMI network is disrupted.^{42,51,77}

Strengths of this review

- The review synthesises fourteen pre-specified outcome domains within a single protocol, permitting the relative magnitude of each component of the primary PCI bundle to be compared on a common footing rather than in isolation.
- The pre-specified separation of stand-alone fibrinolysis from a pharmacoinvasive comparator resolved what would otherwise have been substantial and uninterpretable heterogeneity, and yielded two internally homogeneous subgroups ($I^2 = 0$ per cent in each).
- Every effect estimate not reported directly by a source study was recomputed transparently from the published event counts, and every such derivation is flagged in the relevant table or figure legend; no estimate in this review is imputed, borrowed from a secondary source or otherwise unverifiable.
- Methodological quality was appraised in duplicate with instruments appropriate to each design — RoB 2 for randomised trials and the Newcastle–Ottawa Scale together with ROBINS-I for observational studies — and the certainty of each principal conclusion was rated using GRADE.
- Sensitivity analyses were pre-specified and are reported in full, including those that weakened the review's own conclusions, most notably the loss of statistical significance for the mortality benefit of radial access when a single high-risk-of-bias trial was excluded.
- Each reference is accompanied by a digital object identifier and a permanent Consensus record link, so that every claim in this review can be traced to a verifiable published source.

Implications for practice

- Primary PCI should be the default reperfusion strategy wherever the PCI-related delay can reliably be held below two hours, and every element of the system delay — field triage, pre-hospital electrocardiography, direct catheterisation-laboratory activation bypassing the emergency department — should be optimised, because no lower plateau of benefit has yet been identified.^{35,36,38}
- Where a PCI-related delay of two hours cannot be guaranteed, pre-hospital or district-hospital fibrinolysis followed by routine angiography at six to twenty-four hours is an evidence-based equivalent and should be organised as a formal pathway rather than treated as a failure of the system.^{4,5,43,67}

- Transradial access should be the default for primary PCI in operators and centres with adequate radial experience, principally because of a large and consistent reduction in access-site bleeding and vascular complications and a probable reduction in acute kidney injury.^{20,21,26,60}
- Routine manual thrombus aspiration should not be performed; selective bail-out use in the presence of a very large residual thrombus burden remains defensible but carries a measurable stroke hazard.^{29,30,64}
- New-generation drug-eluting stents should be used in preference to bare-metal stents in all patients, including the elderly, with a benefit that is sustained without late attrition to ten years.^{31,32,69}
- Significant non-culprit lesions should be revascularised during the index hospitalisation, and the operator should aim for anatomical completeness, since the intention to revascularise without its achievement confers no benefit.^{8,12,13,15}
- In cardiogenic shock, the index procedure should be confined to the culprit lesion, with staged revascularisation of remaining lesions thereafter; this recommendation may not extend to patients already supported by veno-arterial extracorporeal membrane oxygenation.^{18,19,72,86}

Implications for research

- A randomised trial comparing immediate with same-admission staged complete revascularisation, adequately powered for hard endpoints and stratified by haemodynamic status, is required to reconcile MULTISTARS AMI with OPTION-STEMI.^{15,16}
- The threshold of PCI-related delay at which primary PCI ceases to be superior to a pharmacoinvasive strategy should be established prospectively in a health system with genuinely long transfer times, rather than inferred from observational modelling.⁴³
- Prognostic models achieving areas under the curve above 0.90 require external validation in independent populations, and their capacity to improve outcomes — not merely to predict them — should be tested in an implementation trial.^{44,49,51}
- Patients presenting between twelve and forty-eight hours after symptom onset, who are systematically excluded from existing trials yet common in health systems with long

patient-related delay, constitute an unaddressed evidence gap of direct relevance to Indonesia and comparable settings.

- The optimal revascularisation strategy for infarct-related cardiogenic shock in patients receiving mechanical circulatory support should be determined by randomised comparison rather than by extrapolation from CULPRIT-SHOCK.^{72,86}

CONCLUSION AND RECOMMENDATIONS

Conclusion

Percutaneous coronary intervention is an efficacious and, on balance, a safe reperfusion strategy for acute ST-segment elevation myocardial infarction, but its benefit is neither uniform nor unconditional. Relative to stand-alone fibrinolysis, primary PCI significantly reduced death-containing composite endpoints in randomised trials (0.85, 95% confidence interval 0.75 to 0.96; $I^2 = 0$ per cent; $p = 0.011$), and this advantage persisted for sixteen years, expressed principally as a forty per cent relative reduction in re-infarction and a 4.4 percentage-point absolute reduction in cardiac death. In contemporary registry practice, where PCI-related delay was kept below sixty minutes, the mortality advantage was more than twice as large (odds ratio 0.38, 0.32 to 0.44; $p < 0.001$). Relative to a pharmacoinvasive strategy, however, primary PCI conferred no advantage (1.20, 0.98 to 1.48; $p = 0.077$), and the mortality benefit of mechanical reperfusion was abolished once the PCI-related delay approached two hours.^{1,2,4,5,43}

Among the adjuncts to primary PCI, complete revascularisation of significant non-culprit lesions reduced cardiovascular death or myocardial infarction (hazard ratio 0.71, 0.54 to 0.91; $p = 0.008$) and approximately halved repeat revascularisation; transradial access reduced mortality (odds ratio 0.64, 0.41 to 0.98; $p = 0.041$) and reduced major bleeding and access-site complications by 4.4 to 5.8 percentage points in absolute terms; and everolimus-eluting stents reduced the device-oriented composite endpoint at ten years (hazard ratio 0.72, 0.55 to 0.93). In the opposite direction, routine manual thrombus aspiration conferred no clinical benefit and significantly increased stroke at one year (hazard ratio 1.66, 1.10 to 2.51; $p = 0.015$), and immediate multivessel intervention in cardiogenic shock increased thirty-day death or renal-replacement therapy relative to a culprit-lesion-only strategy (relative risk 0.83, 0.71 to 0.96 favouring culprit-only PCI; $p = 0.01$). Reperfusion delay showed a consistent monotonic relationship with mortality across every cohort examined, and contemporary prognostic models discriminated in-hospital and thirty-day death

with areas under the receiver-operating-characteristic curve between 0.709 and 0.959. The certainty of the evidence was high for five outcomes, moderate for four and low for three.^{8,12,13,18,20,29,31,35,44,51}

Recommendations

For clinical practice

- Adopt primary PCI as the default reperfusion strategy where a PCI-related delay under two hours is achievable, and treat every minute of system delay as a modifiable determinant of survival.
- Establish a formal pharmacoinvasive pathway — pre-hospital or district-hospital fibrinolysis followed by angiography at six to twenty-four hours — for populations in which that delay threshold cannot be met.
- Use transradial access as the default, new-generation drug-eluting stents in all patients, and index-admission complete revascularisation aiming at anatomical completeness.
- Abandon routine thrombus aspiration, and restrict the index procedure to the culprit lesion in patients presenting with cardiogenic shock.

For health systems and policymakers

- Use the two-hour PCI-related delay threshold as an explicit planning criterion when deciding where to site new catheterisation capacity and where instead to invest in pre-hospital thrombolysis and structured inter-hospital transfer.
- Invest in field triage, pre-hospital electrocardiography and direct catheterisation-laboratory activation, which address the largest modifiable components of total ischaemic time.
- Direct public-awareness efforts at patient-related delay, which in several cohorts exceeded every in-hospital process interval and which disproportionately disadvantages women and older patients.

For researchers

- Prioritise randomised evaluation of the timing of complete revascularisation, of reperfusion strategy in health systems with prolonged transfer times, of PCI beyond twelve hours from symptom onset, and of revascularisation strategy in shock supported by mechanical circulatory support.

- Subject high-performing prognostic models to external validation and to implementation trials that test whether prediction translates into improved outcome.
- Register systematic review protocols prospectively and report sensitivity analyses that weaken as well as those that strengthen the authors' conclusions.

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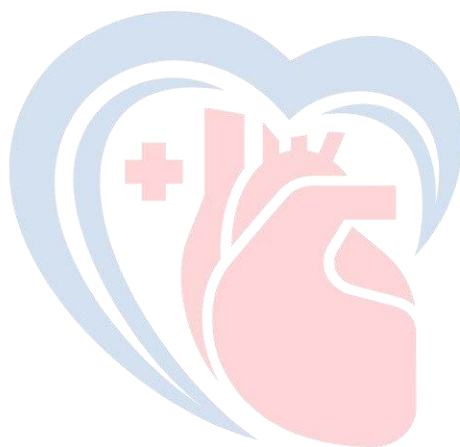
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