The optimal percutaneous coronary intervention strategy for patients with ST-segment elevation myocardial infarction and multivessel disease: a pairwise and network meta-analysis

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Abstract

Objective: To investigate the optimal percutaneous coronary intervention (PCI) strategy in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease.

Methods: Trials that randomized patients with STEMI and multivessel coronary artery disease to immediate multivessel PCI, staged multivessel PCI, or culprit-only PCI and prospective observational studies that investigated all-cause death were included. Random effect risk ratio (RR) and 95% confidence interval (CI) were calculated.

Results: A total of 13 randomized trials with 7627 patients and 21 prospective observational studies with 60311 patients were included. In the pairwise and network meta-analysis based on randomized trials, immediate or staged multivessel PCI was associated with a lower risk of long-term major adverse cardiac events (MACE; RR: 0.58; 95% CI: 0.45 to 0.74) than culprit-only PCI, which was mainly due to lower risks of myocardial infarction (RR: 0.67; 95% CI: 0.51 to 0.88) and revascularization (RR: 0.38; 95% CI: 0.28 to 0.51), without any significant difference in all-cause death (RR: 0.85; 95% CI: 0.69 to 1.04; $I^2 = 0.0\%$). However, short-term outcomes were deficient in randomized trials. The results from real-world prospective observational studies suggested that staged multivessel PCI reduced long-term all-cause death (RR: 0.53; 95% CI: 0.39 to 0.71; $I^2 = 15.6\%$), whereas immediate multivessel PCI increased short-term all-cause death (RR: 1.58; 95% CI: 1.22 to 2.05; $I^2 = 43.8\%$) relative to culprit-only PCI.

Conclusion: For patients in randomized trials, multivessel PCI in an immediate or staged procedure was preferred due to improvements in long-term outcomes. As a supplement, the results in real-world patients derived from prospective observational studies suggested that staged multivessel PCI was superior to immediate multivessel PCI. Therefore, staged multivessel PCI may be the optimal PCI strategy for patients with STEMI and multivessel coronary artery disease.

Keywords: multivessel disease, multivessel revascularization, network meta-analysis, percutaneous coronary intervention, ST-segment elevation myocardial infarction

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Introduction

Primary percutaneous coronary intervention (PCI) remains the cornerstone for the treatment of patients with ST-elevation myocardial infarction (STEMI) when performed in a timely manner.[1] In patients diagnosed with STEMI, it is estimated that approximately 40–65% exhibit multivessel coronary artery disease and are associated with worse short- and long-term mortality and morbidity than subjects with single-vessel disease.[2] Three different revascularization strategies are available for the treatment of multivessel coronary artery disease at the time of primary PCI: (1) immediate multivessel PCI (MV-PCI), in which the infarct-related artery (IRA) and non-IRA are treated during the index procedure; (2) staged MV-PCI strategy, in which the IRA is treated at the index procedure followed by a planned PCI of the non-IRA at a later time within 1 month; and (3) culprit-only PCI (CO-PCI) strategy, in which the only treated vessel is the IRA. The results based on earlier observational studies demonstrated that an immediate MV-PCI strategy was associated with worse short-term outcomes than a CO-PCI strategy.[3,4] However, recent randomized trials including the PRAMI (Preventive Angioplasty in Myocardial Infarction),[5] CvLPRIT (Complete Versus Lesion-Only Primary PCI Trial),[6] DANAMI-3-PRIMULTI (Third Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Primary PCI in Multivessel Disease),[7] COMPARE-ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel Coronary Artery Disease),[8] and COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trials[9] as well as meta-analyses[10,11] all demonstrated that immediate or staged MV-PCI was superior to CO-PCI in reducing the risks of long-term revascularization, cardiac death and myocardial infarction in the absence of short-term outcomes. Therefore, the utility and strategy of MV-PCI in patients with STEMI and multivessel coronary artery disease remain difficult to perform in real-world practice in China.[12] Meanwhile, differences exist with regard to the guidance [angiography or fractional flow reserve (FFR)] of non-IRA revascularization. Thus, we sought to conduct a comprehensive pairwise and network meta-analysis of randomized trials to assess the relative merits of different PCI strategies in patients with STEMI and multivessel coronary artery disease, and subgroups were designed based on the guidance of revascularization (angiography or FFR) and MV-PCI strategy (Immediate, staged or mixed). Moreover, considering that many early deaths occur within several days after STEMI[13] and that short-term outcomes were not reported in randomized trials, we resorted to prospective observational studies to investigate short-term (in-hospitalization or within 30 days) and long-term all-cause death (≥6 months) among different PCI revascularization strategies.

Methods

Data sources

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for pairwise and network meta-analysis.[14,15] An electronic search of PubMed, Web of Science, the Cochrane Library, ClinicalTrials.gov, and Google Scholar along with major conference proceedings was conducted using the Medical Subject Heading and the keyword search terms 'percutaneous coronary intervention(MESH)', 'myocardial infarction(MESH)', 'PCI', 'angiography', 'STEMI', 'multivessel', 'non-IRA', 'culprit-only', 'staged', 'immediate', 'simultaneous', 'incomplete' and 'complete revascularization' from inception through November 2020 with no language restriction. In addition, we searched the presentations at major cardiovascular scientific sessions and the bibliographies of original trials, meta-analyses, and review articles to find other eligible studies. This meta-analysis was registered at the PROSPERO international prospective register of systematic reviews (CRD42020218552). We obtained summary data from published studies, which has been approved by the institutional review committee in their respective studies. Therefore, no further sanction was required for our meta-analysis.

Selection criteria

We only included randomized trials and prospective observational studies (observational studies must investigate all-cause death) that compared any combination of CO-PCI, immediate MV-PCI

or staged MV-PCI in patients with STEMI and multivessel coronary artery disease. Studies focused on patients diagnosed with cardiogenic shock or chronic total occlusion (CTO) were excluded to ensure similar baseline characteristics. The quality of the included randomized trials was evaluated using Review Manager 5.3.

Data extraction

Two independent authors (M.-J.H. and J.-S.T.) extracted information regarding the study design, interventions performed, number and characteristics of patients enrolled, definition of multivessel coronary artery disease, inclusion and exclusion criteria, clinical outcomes, follow-up duration and baseline characteristics of the included patients. Any discrepancies were resolved by consensus with third-party adjudication (X.-J.G.).

Outcomes

In analyses based on randomized trials, the primary outcomes were major adverse cardiac events (MACE), all-cause death, myocardial infarction and revascularization. We preferentially utilized data from the longest available follow-up as long-term outcomes. Secondary outcomes defined as cardiac death, angina, heart failure and rehospitalization together with safety outcomes defined as major bleeding, renal failure and stroke were also investigated. In prospective observational studies, short- and long-term all-cause death were investigated.

Statistical analysis

Raw, unadjusted data from the included randomized trials and prospective observational studies were extracted. Random-effects models of DerSimonian and Laird were used to construct the summary estimated risk ratio (RR) and the corresponding 95% confidence interval (CI). Statistical heterogeneity was examined using the I^2 statistic, with I^2 being considered substantial when it was >50%.[16] Begg's method and funnel plot were used to estimate publication bias.[17] Sensitivity analysis was performed using a leave-one-out analysis to assess whether the pooled results were influenced by a single trial. All analyses for the pairwise meta-analysis were performed using STATA software version 14 (STATA Corporation, College Station, Texas). Meanwhile,

network meta-analysis was carried out using the 'network' command in STATA software.[18] We performed trial sequential analysis (TSA) to assess the reliability and conclusiveness of the present evidence, anticipating a 25% RR reduction for efficacy outcomes, $\alpha = 5\%$, $1 - \beta = 80\%$.[19] TSA was conducted using TSA software, version 0.9 beta (Copenhagen Trial Unit, Copenhagen, Denmark).

Results

Search process, study characteristics and quality assessment

Our initial search yielded 5286 articles. Ultimately, 13 randomized trials enrolling 7627 patients and 21 prospective observational studies enrolling 60311 patients met our inclusion criteria. Figure 1 reports how the eligible studies were identified. Table 1 reports the characteristics of the included randomized trials. Overall, two trials[5,20] compared immediate MV-PCI with CO-PCI, four trials[6,8,21,22] compared mixed MV-PCI (either immediate or staged) with CO-PCI, five trials[7,9,23–25] compared staged MV-PCI with CO-PCI and two trials[26,27] compared staged MV-PCI with immediate MV-PCI. Meanwhile, in three trials,[7,8,23] non-IRA was revascularized with the guidance of FFR. Table 2 summarizes the baseline characteristics of the included patients. The patients were more likely to be old males with a history of hypertension and diabetes. Over time, more drug-eluting stents (DES) were adopted. Figure 2(a)–(d) and Figure 2(e) and (f) report the evidence of the included randomized trials and prospective observational studies, respectively. Figure 2(g) summarizes the measures of study quality. The characteristics of the included prospective observational studies are shown in Supplementary Table 1.

Pairwise meta-analysis of MACE, myocardial infarction and revascularization based on randomized trials

Compared with CO-PCI, MV-PCI was associated with lower risks of long-term MACE (RR: 0.58; 95% CI: 0.45 to 0.74; $I^2 = 57.0\%$), myocardial infarction (RR: 0.67; 95% CI: 0.51 to 0.88; $I^2 = 18.8\%$) and revascularization (RR: 0.38; 95% CI: 0.28 to 0.51; $I^2 = 63.5\%$) (Supplementary
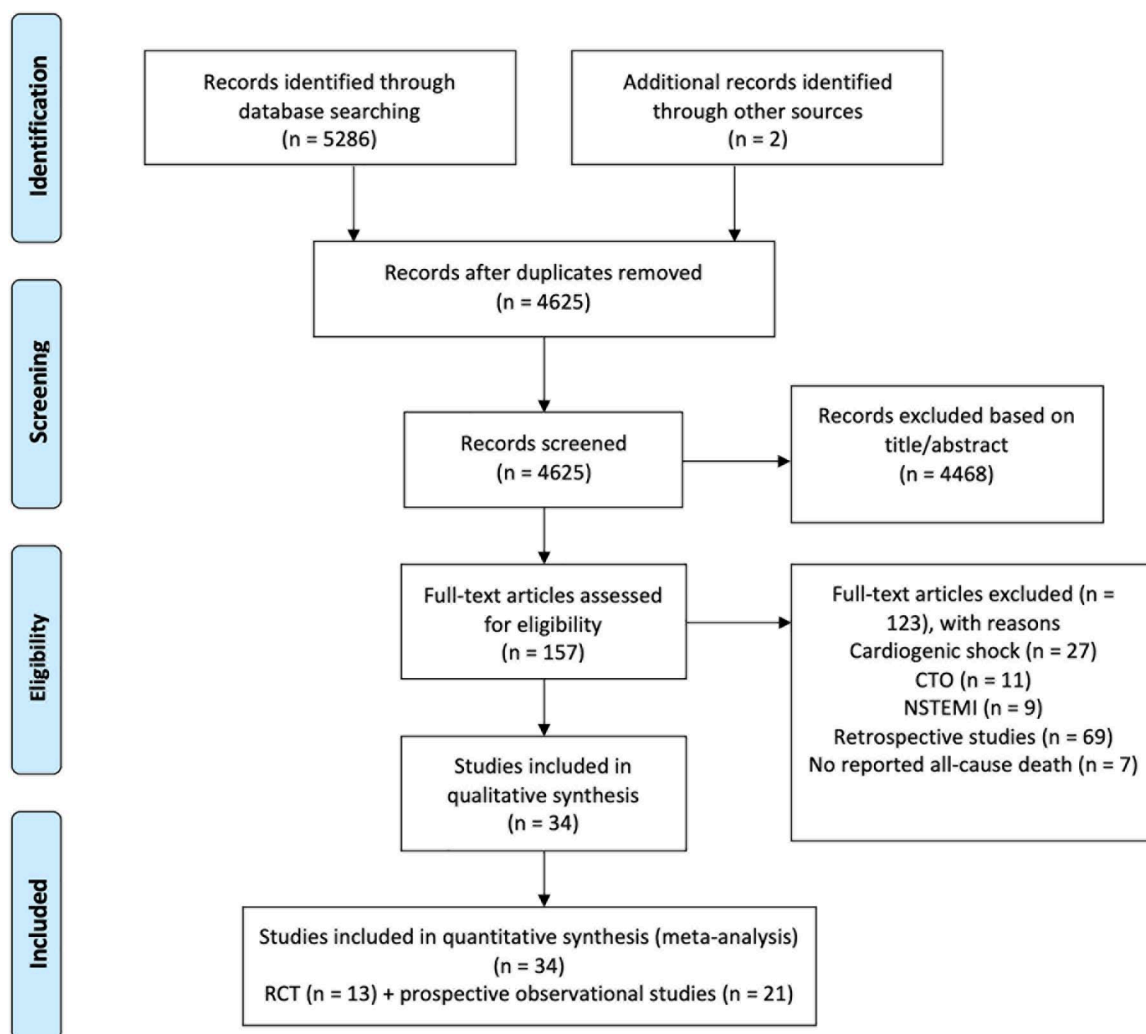
Figure 1. PRISMA flow of the study search.
CTO, chronic total occlusion; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Figures 1–3), which were not influenced by the strategy (immediate, staged or mixed) or the guidance of MV-PCI.

Pairwise meta-analysis of all-cause death based on randomized trials and prospective observational studies, respectively

Analyses based on randomized trials revealed that the risk of all-cause death was similar between MV-PCI and CO-PCI (RR: 0.85; 95% CI: 0.69 to 1.04; $I^2 = 0.0\%$) (Figure 3). However, analyses based on prospective observational studies suggested that compared with CO-PCI, immediate MV-PCI increased the risk of short-term all-cause death (RR: 1.58; 95% CI: 1.22 to 2.05; $I^2 = 43.8\%$), whereas the risk of long-term all-cause death (RR: 1.15; 95% CI: 0.83 to 1.58; $I^2 = 91.6\%$) was similar (Figure 4(a)). The risk of short-term all-cause death (RR: 0.29; 95% CI: 0.03 to 2.58; $I^2 = 62.0\%$) was similar between staged MV-PCI and CO-PCI, yet staged MV-PCI decreased the risk of long-term all-cause death (RR: 0.53; 95% CI: 0.39 to 0.71; $I^2 = 15.6\%$) (Figure 4(b)). Immediate MV-PCI increased the risks of both short-term (RR: 3.11; 95% CI: 2.11 to 4.57; $I^2 = 0\%$) and long-term all-cause death (RR: 2.24; 95% CI: 1.37 to 3.66; $I^2 = 80.1\%$) compared with staged MV-PCI (Figure 4(c)).

Meta-regression based on randomized trials

The publication year of the study, age, sex, hypertension, diabetes, radial access, DES and

Table 1. Main characteristics of included randomized trials.

Trial/first author year	Setting	PCI strategies subgroups, n			Timing of staged MV-PCI	Definition of MVD	Inclusion criteria	Exclusion criteria	Primary endpoints	Follow-up time
		CO-PCI	Immediate MV-PCI	Staged MV-PCI						
HELP AMI[20] 2004	Multicenter	17	52	NA	NA	NA	The presence of ischemic chest pain started less than 12h before hospital admission and ST-segment elevation of at least 1mm in ≥2 electrocardiographic leads (peripheral leads) or 2mm in the precordial leads	The presence of significant lesions in vein grafts or arterial conduits or in segments previously treated with angioplasty or stent implantation, recent thrombolysis (<1week), cardiogenic shock	Revascularization	12months
Politi et al.[21]	Single centre	84	65	65	56.8 ± 12.9 days	>70% diameter stenosis of ≥2 epicardial coronary arteries or their major branches by visual estimation	The presence of prolonged (>30min) chest pain, started <12h before hospital arrival and ST-elevation of at least 1mm in ≥2 contiguous limb electrocardiographic leads or 2mm in precordial leads	Cardiogenic shock, LM disease, previous CABG, severe valvular heart disease and unsuccessful procedures	MACE defined as cardiac or non-cardiac death, in-hospital death, re-infarction, rehospitalization for acute coronary syndrome and repeat coronary revascularization	2.5 ± 1.4 years
Maamoun et al.[26]	Single centre	NA	42	36	Within 7 days	≥2 angiographically documented diseased coronary arteries (luminal diameter narrowing ≥70%)	STEMI presented within 12h from the onset of symptom with MVD and received primary PCI	Cardiogenic shock, pulmonary edema and LM disease	MACE including death (cardiac or non-cardiac), re-infarction, rehospitalization for recurrent angina, TVR and cerebrovascular accidents	12months
Ghani et al.[23]	Single centre	41	NA	80	In-hospital or in an outpatient setting within 3weeks after STEMI	≥2.5mm diameter stenosis of ≥50% in ≥2 major epicardial coronary arteries	Patients with multivessel disease who underwent successful primary angioplasty for STEMI	Urgent indication for additional revascularization, >80years old, CTO of one of the non-IRA, previous CABG, LM stenosis of ≥50%, restenotic lesions in non-IRA, chronic atrial fibrillation, limited life expectancy, other factors that made complete follow-up unlikely	Ejection fraction at 6months	3 years

(Continued)

Table 1. (Continued)

Trial/first author year	Setting	PCI strategies subgroups, n			Timing of staged MV-PCI	Definition of MVD	Inclusion criteria	Exclusion criteria	Primary endpoints	Follow-up time
		CO-PCI	Immediate MV-PCI	Staged MV-PCI						
PRAMI[5] 2013	Multicentre	231	234	NA	NA	Stenosis of ≥50% in ≥1 coronary artery other than the IRA	IRA had been treated successfully and there was stenosis of 50% or more in ≥1 coronary artery other than the IRA and the stenosis was deemed to be treatable by PCI	Cardiogenic shock, unable to provide consent, previous CABG, non-IRA stenosis of ≥50% in the LM or the ostia of both the left anterior descending and circumflex arteries, or the only noninfarct stenosis was a CTO	Composite of death from cardiac causes, nonfatal myocardial infarction or refractory angina	23 months
Roman *et al.*[27]	Single centre	NA	46	43	8.5 ± 4.2 days	≥70% diameter stenosis of ≥2 epicardial coronary arteries or their major branches by visual estimation with diameter ≥2.5 mm	≥18 years, provided written informed consent prior to any study-related procedure, significant stenoses (≥70%) of ≥2 of coronary arteries and requiring primary PCI for STEMI within 12h, target lesions located in a native coronary artery with visually estimated diameter of 2.5–4.0 mm, amenable for PCI	Single lesions, acute heart failure Killip III-IV, ≥50% LM stenosis, small vessels diameter (<2.5 mm), hypersensitivity or contraindication to any of the following medications: Heparin Aspirin Both Clopidogrel and Ticlopidine, Zotarolimus	All death (cardiac and non-cardiac), any MI (STEMI and non-STEMI), TVR	6 months
DANAMI-3-PRIMULTI[7] 2015	Multicentre	313	NA	314	2 days after the initial PCI procedure before discharge	Angiographic diameter stenosis of ≥50% in ≥1 non-IRA of 2 mm or larger in diameter	Chest pain of <12h duration and ST-segment elevation >0.1 mV in ≥2 contiguous leads, successful treatment of IRA	Intolerance of contrast media or of relevant anticoagulant or antithrombotic drugs, unconsciousness or cardiogenic shock, stent thrombosis, indication for CABG, or increased bleeding risk	Composite of all-cause mortality, re-infarction, or ischaemia-driven (subjective or objective) revascularization of lesions in non-IRA	27 months
CvLPRIT[6] 2015	Multicentre	146	97	42	Before hospital discharge	>70% diameter stenosis in one plane or >50% in two planes, the non-IRA should be a major (>2 mm) epicardial coronary artery or branch (>2 mm)	Patients presented within 12h of symptom onset with MVD and non-IRA stenosis >70%	Any exclusion criteria for P-PCI, <18 years, contraindication to multi vessel P-PCI according to operator judgement, previous Q wave MI, prior CABG, cardiogenic shock, VSD or moderate/severe mitral regurgitation, chronic kidney disease, suspected or confirmed thrombosis of a previously stented artery, the only significant no-IRA lesion is a CTO	MACE comprising all-cause mortality, recurrent MI, heart failure, and ischemic-driven revascularization by PCI/CABG	5.6 years

(Continued)

Table 1. (Continued)

Trial/first author year	Setting	PCI strategies subgroups, *n*			Timing of staged MV-PCI	Definition of MVD	Inclusion criteria	Exclusion criteria	Primary endpoints	Follow-up time
		CO-PCI	Immediate MV-PCI	Staged MV-PCI						
Zhang et al.[24]	Single centre	213	NA	215	Within 7–10 days after AMI	Angiographic diameter stenosis of 75–90% in ≥1 non-IRA of 2.5 mm or larger in diameter	STEMI with MVD, stenosis of 75–90% in ≥1 non-IRA of 2.5 mm or larger in diameter	Cardiogenic shock, prior CABG, unconfirmed IRA, patients refused further PCI, the significant no-IRA lesion is a CTO, stenosis >90%	MACE defined as recurrent MI and cardiac death	24 months
PRAGUE 13[25] 2015	Multicentre	108	NA	106	3–40 days after PPCI	≥1 significant (≥70%) stenosis of non-IRA	STEMI, successful primary PCI of IRA (TIMI flow grades II–III], ≥1 stenosis (≥70%) of non-IRA (diameter of artery ≥2.5 mm) found by coronary angiography, enrolment ≥48 h following onset of symptoms	Stenosis of the LM ≥50%, hemodynamically significant valvular disease, cardiogenic shock during STEMI, hemodynamic instability, angina pectoris >grade 2 CCS lasting 1 month prior to STEMI	MACE defined as all-cause mortality, nonfatal MI, stroke	38 months
Hamza et al.[22]	Multicentre	50	29	21	Within 72 h during hospitalization	Angiographic stenosis ≥80% in non-IRA	STEMI with MVD in patients with diabetes within 12 h of symptoms	Lesions from 50% to 70% stenosis, CTO of one of the non-IRA, previous CABG or LM stenosis >50%	The composite of all-cause mortality, recurrent MI, and ischaemia-driven revascularization at 6 months	6 months
Compare-Acute[8] 2017	Multicentre	590	295	NA	Generally during the same intervention, delayed had to be during index hospitalization and preferably within 72 h	NonIRA (or their major side branches of ≥2.0 mm in diameter) showed stenosis ≥50%	STEMI with MVD that was appropriate for FFR and PCI	LM disease, CTO, severe stenosis, TIMI flow grade ≤2 in the non-IRA, a suboptimal result or complications after treatment of an IRA, severe valve dysfunction, and Killip class III or IV	The composite of all-cause mortality, nonfatal myocardial infarction, any revascularization and MACCE	12 months
COMPLETE[9] 2019	Multicentre	2025	NA	2016	Index hospitalization or after hospital discharge within 45 days after randomization	≥1 angiographically significant non-IRA lesion (≥70% stenosis of the vessel diameter on visual estimation or with 50–69% stenosis .accompanied by FFR ≤0.80) and vessel diameter ≥2.5 mm	Presented to the hospital with STEMI and could undergo randomization within 72 h after successful culprit-lesion PCI	An intention before randomization to revascularize a non-IRA lesion, a planned surgical revascularization, or previous CABG	The composite of death from cardiovascular causes or new myocardial infarction	3 years

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; Compare-Acute, Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel Coronary Artery Disease; COMPLETE, Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI; CO-PCI, culprit-only percutaneous coronary intervention; CTO, chronic total occlusion; CvLPRIT, Complete Versus Lesion-Only Primary PCI Trial; DANAMI-3-PRIMULTI, Third Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Primary PCI in Multivessel Disease; FFR, fractional flow reserve; HELP AMI, HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction; IRA, infarct-related coronary artery; LM, left main coronary artery; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; MI, myocardial infarction; MVD, multivessel disease; MV-PCI, multivessel percutaneous coronary intervention; PCI, percutaneous coronary intervention; PRAM, Preventive Angioplasty in Myocardial Infarction; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization; VSD, ventricular septal defect.
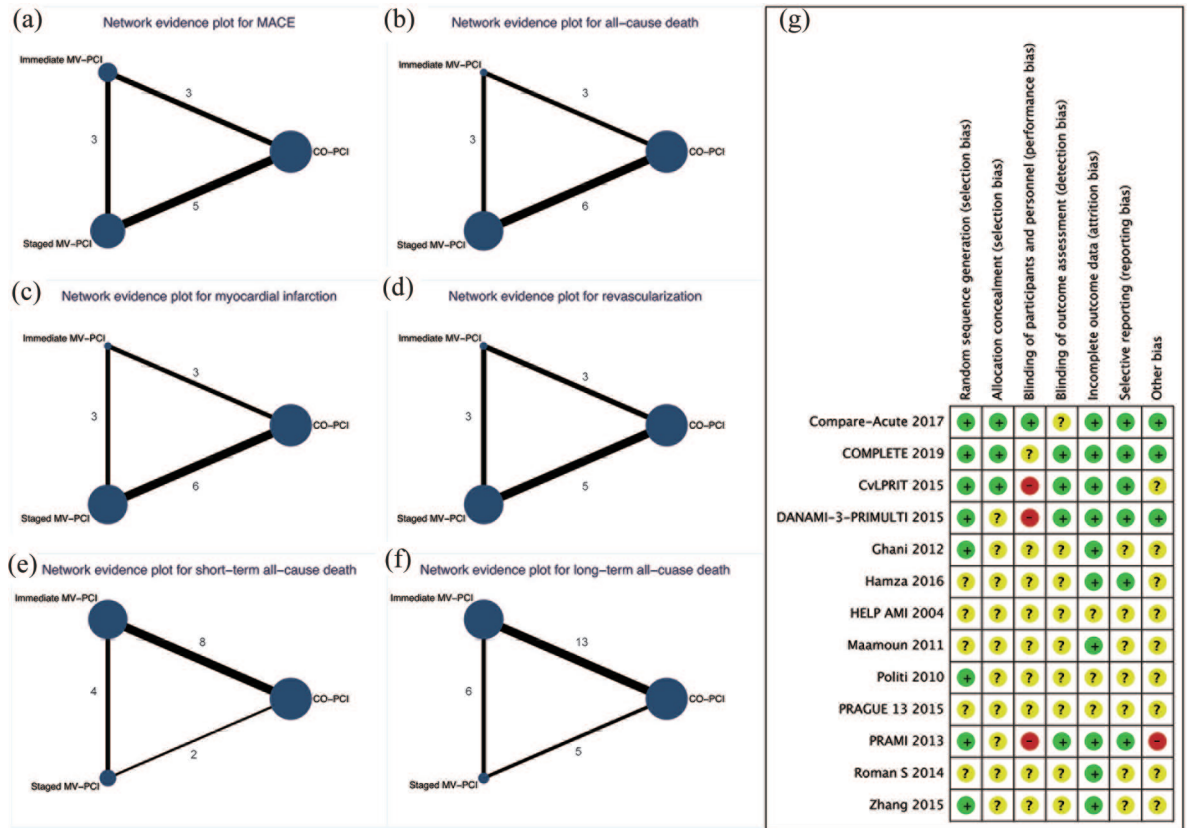
Figure 2. Network evidence and risk of bias of included studies. Network evidence plot for primary outcome of randomized trials (a–d), all-cause death of prospective observational studies (e and f), and risk of bias of included randomized trials (g).

administration of glycoprotein IIb/IIIa inhibitor were not associated with long-term MACE, all-cause death, myocardial infarction or revascularization results. However, there was a trend that the prevalence of three-vessel disease was positively associated with MACE ($p = 0.086$) (Supplementary Table 2).

Pairwise meta-analysis of secondary and safety outcomes based on randomized trials

Compared with CO-PCI, MV-PCI (immediate or staged) was associated with lower risks of long-term cardiac death (RR: 0.73; 95% CI: 0.54 to 0.98; $I^2 = 6.6\%$), angina (RR: 0.49; 95% CI: 0.39 to 0.61; $I^2 = 0.0\%$) and rehospitalization (RR: 0.44; 95% CI: 0.29 to 0.66; $I^2 = 4.9\%$). The risk of long-term heart failure was similar between MV-PCI and CO-PCI (Supplementary Figure 4). Safety outcomes including major bleeding, renal failure and stroke were also similar between

MV-PCI and CO-PCI (Supplementary Figure 5). The results of the sensitivity analyses were consistent with the main analyses (Supplementary Figure 6). There was no evidence of publication bias (Supplementary Figures 7).

TSA results of randomized trials

Regarding MACE, myocardial infarction and revascularization, the cumulative z-curve crossed both the conventional boundary ($p = 0.05$) and the trial sequential boundary, indicating that compared with CO-PCI, MV-PCI reduced the risks of long-term MACE, myocardial infarction and revascularization by 25% with firm evidence (Figure 5). However, regarding all-cause death, the cumulative z-curve crossed the futility boundary, indicating that MV-PCI failed to reduce the risk of long-term all-cause death by 25% compared with CO-PCI. The TSA results for secondary and safety outcomes are shown in Supplementary Figures 8 and 9, respectively.

Table 2. Baseline characteristics of included patients in randomized trials.

Trial/first author year	Group	Age, years	Male, %	Hypertension, %	Diabetes, %	Three-vessel diseases, %	Radial approach, %	DES, %	GpIIb/IIIa inhibitors, %
HELP AMI[20] 2004	CO-PCI	65.3 ± 7.4	84.6	58.8	41.2	47.1	NA	NA	82.4
	Immediate MV-PCI	63.5 ± 12.4	88.2	36.5	11.5	30.8	NA	NA	75.0
	Staged MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
Politi *et al.*[21]	CO-PCI	66.5 ± 13.2	76.2	59.5	23.8	25.0	NA	11.9	NA
	Immediate MV-PCI	64.5 ± 11.7	76.9	49.2	13.8	29.2	NA	7.7	NA
	Staged MV-PCI	64.1 ± 11.1	80.0	64.6	18.5	44.6	NA	9.2	NA
Maamoun *et al.*[26]	CO-PCI	NA	NA	NA	NA	NA	NA	NA	NA
	Immediate MV-PCI	54.52 ± 10.3	95.2	38.1	40.5	26.2	NA	35.7	NA
	Staged MV-PCI	52.33 ± 7.1	88.9	33.3	55.6	22.2	NA	31.7	NA
Ghani *et al.*[23]	CO-PCI	61 ± 11	80.5	42.5	5.0	19.5	NA	17.1	46.3
	Immediate MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
	Staged MV-PCI	62 ± 10	80.0	26.3	6.3	25.0	NA	22.5	45.0
PRAMI[5] 2013	CO-PCI	62	81	40	21	33	NA	58	76
	Immediate MV-PCI	62	76	40	15	39	NA	63	76
	Staged MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
Roman *et al.*[27]	CO-PCI	NA	NA	NA	NA	NA	NA	NA	NA
	Immediate MV-PCI	58.6 ± 11	69.6	95.6	26.1	43.5	43.5	NA	NA
	Staged MV-PCI	58.9 ± 10.4	58.1	86	20.9	46.5	53.5	NA	NA
DANAMI-3-PRIMULTI[7] 2015	CO-PCI	63	81	47	13	32	NA	93	23
	Immediate MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
	Staged MV-PCI	64	80	41	9	31	NA	95	20

(Continued)

Table 2. (Continued)

Trial/first author year	Group	Age, years	Male, %	Hypertension, %	Diabetes, %	Three-vessel diseases, %	Radial approach, %	DES, %	GpIIb/IIIa inhibitors, %
CvLPRIT[6] 2015[a]	CO-PCI	65.3 ± 11.9	76.7	36.4	14.3	24.7	72.9	90.7	31.7
	Immediate MV-PCI	64.6 ± 11.2	85.3	36.6	12.9	20.7	76.7	95.9	31.7
	Staged MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
Zhang et al.[24]	CO-PCI	61.88 ± 11.71	67.1	61.0	35.2	NA	NA	100	38.0
	Immediate MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
	Staged MV-PCI	62.25 ± 9.96	60.9	64.2	36.7	NA	NA	100	35.3
PRAGUE 13[25] 2015	CO-PCI	NA	NA	NA	NA	NA	NA	NA	NA
	Immediate MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
	Staged MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
Hamza et al.[22,a]	CO-PCI	52.2 ± 10.6	86	36	100	34	46	NA	34
	Immediate MV-PCI	56.4 ± 11.5	82	26	100	28	42	NA	38
	Staged MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
Compare-Acute[8] 2017[a]	CO-PCI	61 ± 10	76.3	47.8	15.9	32.9	NA	NA	NA
	Immediate MV-PCI	62 ± 10	79	46.1	14.6	30.8	NA	NA	NA
	Staged MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
COMPLETE[9] 2019	CO-PCI	62.4 ± 10.7	79.1	50.7	19.9	22.9	80.7	NA	NA
	Immediate MV-PCI	NA	NA	NA	NA	NA	NA	NA	NA
	Staged MV-PCI	61.6 ± 10.7	80.5	48.7	19.1	23.9	80.8	NA	NA

AMI, acute myocardial infarction; Compare-Acute, Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel Coronary Artery Disease; COMPLETE, Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI; CO-PCI, culprit-only percutaneous coronary intervention; CvLPRIT, Complete Versus Lesion-Only Primary PCI Trial; DANAMI-3-PRIMULTI, Third Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Primary PCI in Multivessel Disease; DES, drug-eluting stents; HELP AMI, HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction; MV-PCI, multivessel percutaneous coronary intervention; PRAMI, Preventive Angioplasty in Myocardial Infarction.
[a]MV-PCI was performed either immediately or staged and results were mixed, and the results were shown in the group that included more patients.
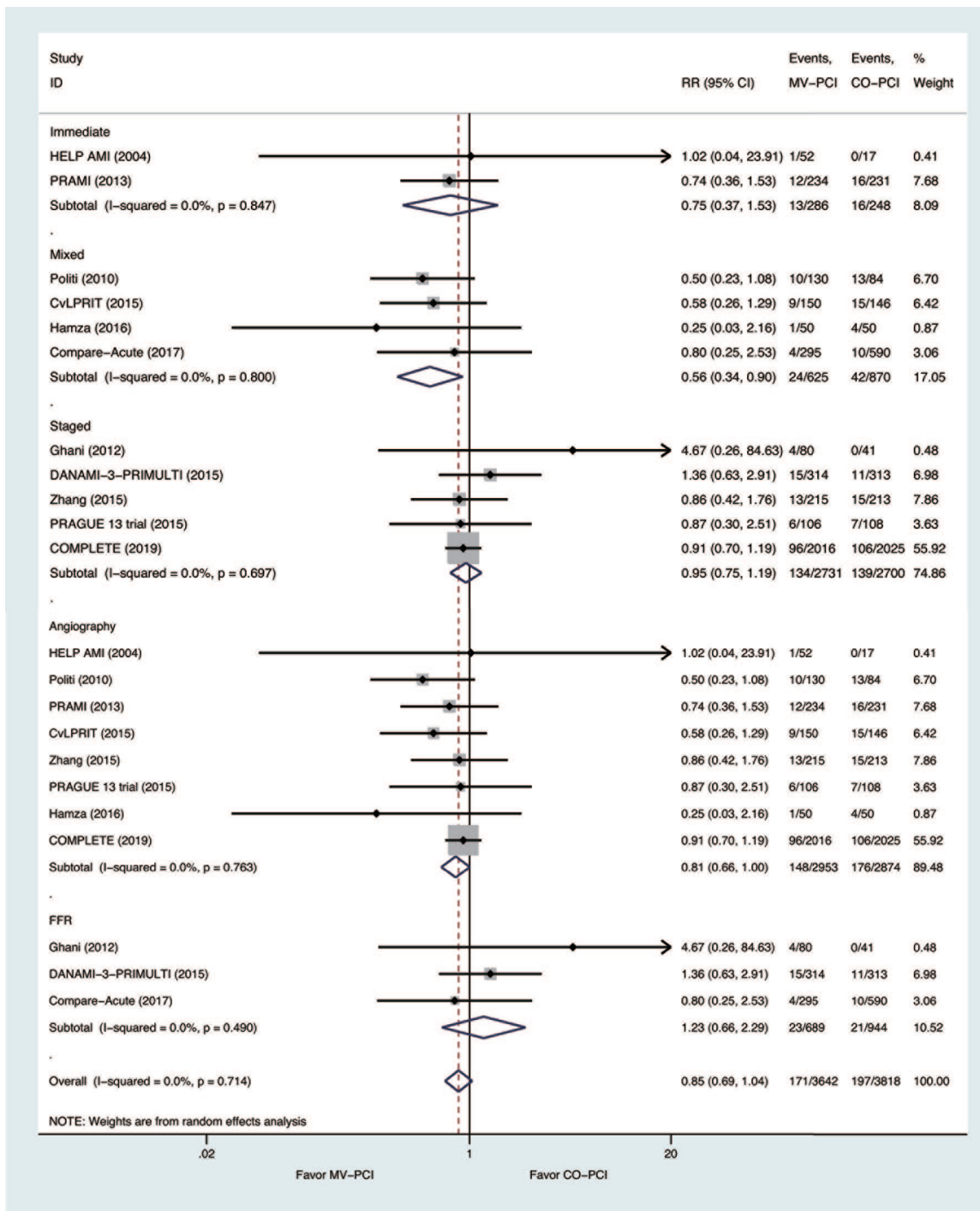
Figure 3. Pairwise meta-analysis of long-term all-cause death based on randomized trials.

Network meta-analysis of randomized trials
The mixed treatment model showed that MV-PCI in an immediate or staged procedure was associated with lower risks of long-term MACE, myocardial infarction and revascularization than CO-PCI. However, there was no significant difference between immediate and staged MV-PCI regarding MACE, myocardial infarction and revascularization. The risk of long-term all-cause death was similar between any combination of the three different revascularization strategies (Figure 6(a)). CO-PCI showed the

(a)

(b)

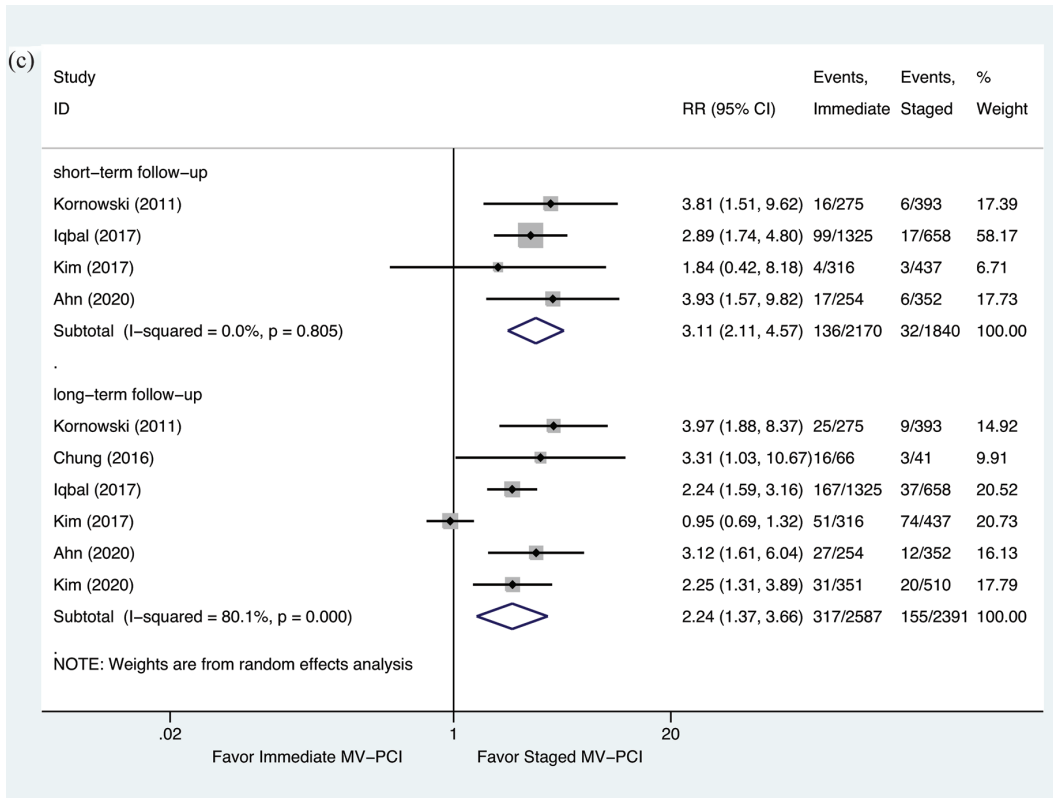**Figure 4.** *(Continued)*

(c)

Study ID		RR (95% CI)	Events, Immediate	Events, Staged	% Weight
short–term follow–up					
Kornowski (2011)		3.81 (1.51, 9.62)	16/275	6/393	17.39
Iqbal (2017)		2.89 (1.74, 4.80)	99/1325	17/658	58.17
Kim (2017)		1.84 (0.42, 8.18)	4/316	3/437	6.71
Ahn (2020)		3.93 (1.57, 9.82)	17/254	6/352	17.73
Subtotal (I–squared = 0.0%, p = 0.805)		3.11 (2.11, 4.57)	136/2170	32/1840	100.00
.					
long–term follow–up					
Kornowski (2011)		3.97 (1.88, 8.37)	25/275	9/393	14.92
Chung (2016)		3.31 (1.03, 10.67)	16/66	3/41	9.91
Iqbal (2017)		2.24 (1.59, 3.16)	167/1325	37/658	20.52
Kim (2017)		0.95 (0.69, 1.32)	51/316	74/437	20.73
Ahn (2020)		3.12 (1.61, 6.04)	27/254	12/352	16.13
Kim (2020)		2.25 (1.31, 3.89)	31/351	20/510	17.79
Subtotal (I–squared = 80.1%, p = 0.000)		2.24 (1.37, 3.66)	317/2587	155/2391	100.00

NOTE: Weights are from random effects analysis

.02   1   20

Favor Immediate MV–PCI   Favor Staged MV–PCI

Figure 4. Pairwise meta-analysis of all-cause death based on prospective observational studies. (a) Immediate MV-PCI vs Culprit-only PCI, (b) Staged MV-PCI vs Culprit-only PCI, and (c) Immediate MV-PCI vs Staged MV-PCI.
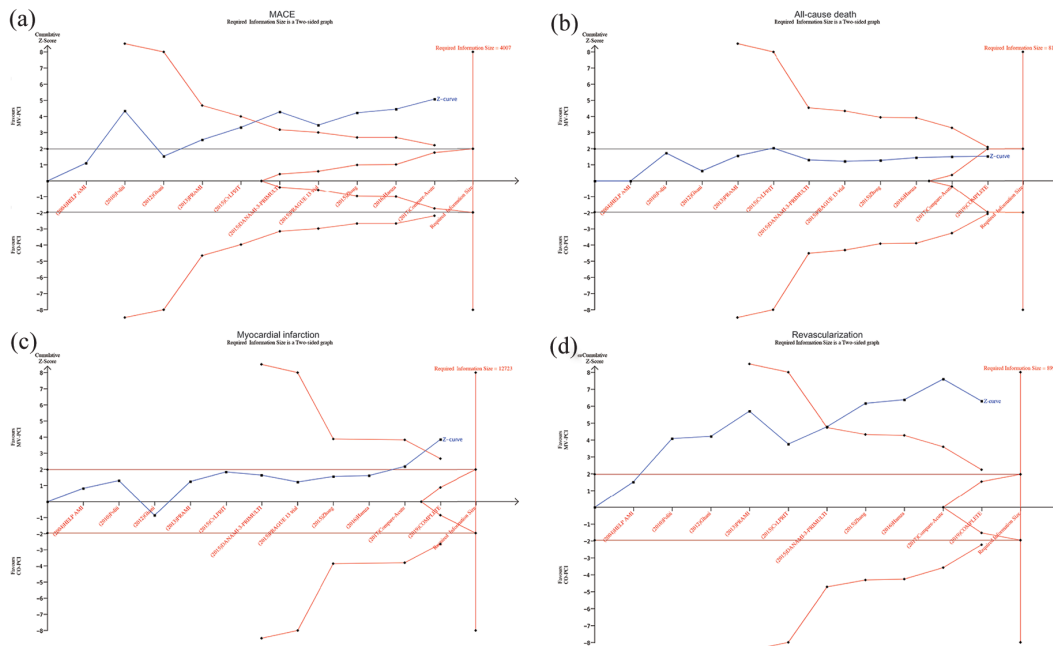
Figure 5. Results of the TSA for the risks of long-term primary outcomes based on randomized trials. (a) MACE, (b) All-cause death, (c) Myocardial infarction, and (d) Revascularization.
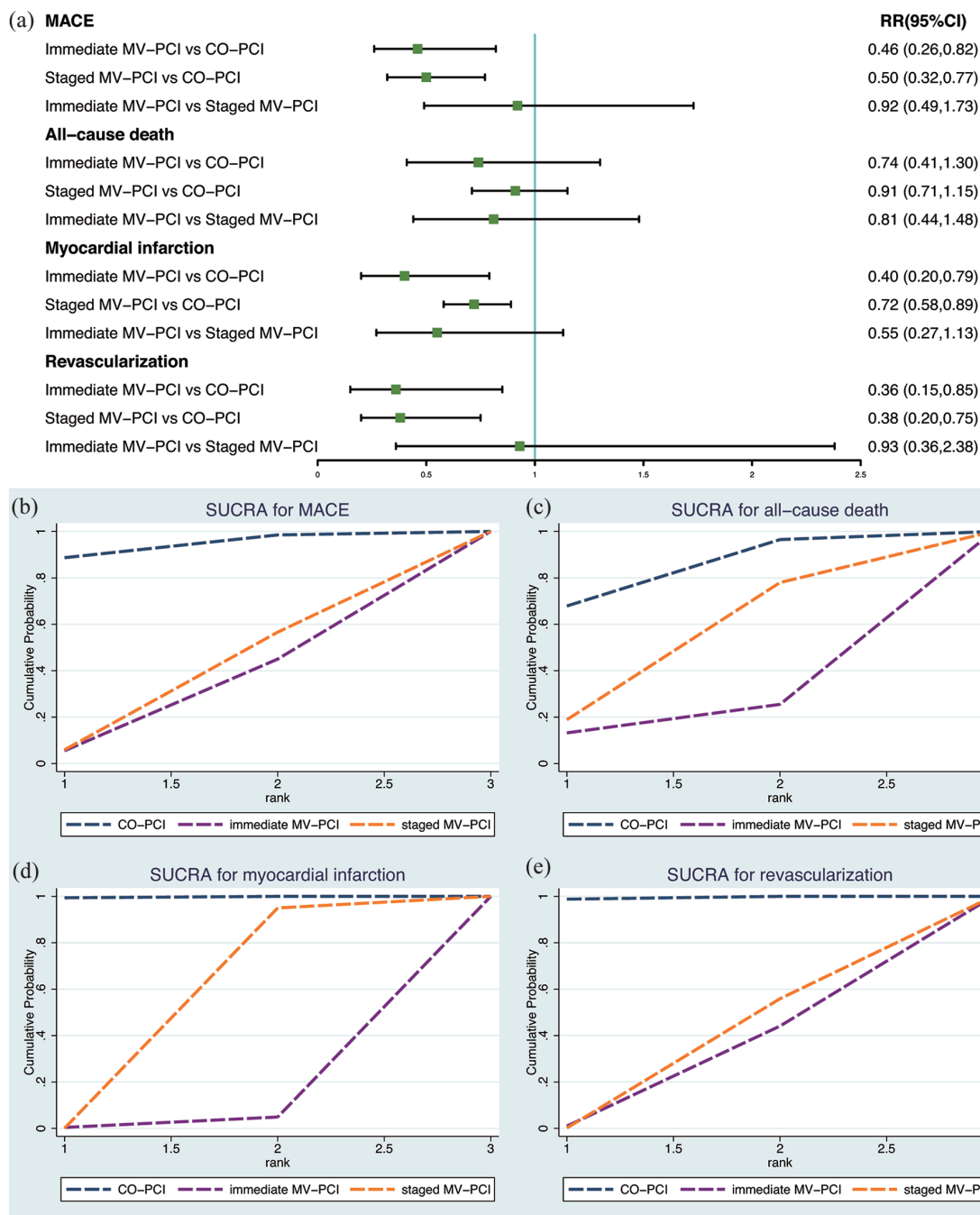TSA, trial sequential analysis.

Figure 6. Forest plot and cumulative probability rankings for the network meta-analysis. Forest plot for the network meta-analysis (a) and cumulative probability rankings (b–e) for long-term primary outcomes based on randomized trials.

highest cumulative probability for increasing the risks of long-term MACE, all-cause death, myocardial infarction and revascularization, followed by staged and immediate MV-PCI strategies (Figure 6(b)–(e)). The contribution, loop consistency, comparison-adjusted and predictive interval plots for network meta-analysis are shown in Supplementary Figures 10–13, respectively.

Discussion

In the meta-analysis based on randomized trials, we demonstrated that MV-PCI (immediate or staged) was associated with a 42% lower risk for long-term MACE, which was mainly due to a 33% lower risk for myocardial infarction and a 62% lower risk for revascularization. The results above were consistent with the network meta-analysis. However, real-world prospective observational studies suggested that staged MV-PCI decreased both short- and long-term all-cause death, whereas immediate MV-PCI increased the risk of short-term all-cause death relative to CO-PCI.

Our results are consistent with previous meta-analyses of randomized trials suggesting that MV-PCI was associated with reduced MACE.[28–30] However, these analyses focused on comparing pooled MV-PCI with CO-PCI rather than exploring the relative benefit from immediate MV-PCI *versus* staged MV-PCI. This comparison is significant, as immediate MV-PCI is different from staged MV-PCI from both technical and pathophysiological perspectives.[31,32] Moreover, immediate and staged MV-PCI strategies have some individual advantages and disadvantages.[33] In our pairwise and network meta-analysis of randomized trials, we did not find that the timing of MV-PCI (immediate or staged) had an impact on long-term clinical outcomes, which means there was a consistent treatment effect for MV-PCI *versus* CO-PCI, regardless of the timing when MV-PCI was achieved. Meanwhile, the largest randomized trial in the field at present, the COMPLETE trial,[34] showed that the benefit of MV-PCI over CO-PCI was consistent irrespective of the timing of non-IRA intervention (index hospitalization or after hospital discharge). Therefore, achieving MV-PCI, rather than its timing, is the most important determinant of long-term clinical outcomes according to the results of randomized trials.

It is noteworthy that in our included randomized trials, patients were strictly selected, and those with high-risk conditions such as cardiogenic shock, left main coronary artery disease and CTO were excluded from 12 of the included 13 studies. Therefore, the included patients in randomized trials represented strictly selected patients with relatively low-risk profiles compared with patients from real-world scenarios, and caution is advised

when extrapolating our findings to real-world populations. Meanwhile, short-term all-cause death within hospitalization or 30 days was not reported, and we are unable to exclude the possibility that the higher rates of long-term MACE and revascularization in the CO-PCI group could be a consequence of competing risks. After all, the pathological inflammatory process in STEMI involves not only the IRA but also the entire coronary tree and can lead to the destabilization and rupture of multiple atherosclerotic plaques, resulting in a sharply increased risk of death.[35] Worse still, the dynamics of this specific inflammatory process are greatest in the first month after STEMI.[36,37] If patients receive immediate MV-PCI, unforeseen periprocedural complications in the non-IRA region may be poorly tolerated due to the 'double jeopardy' of the IRA and non-IRA regions.[31] Increased radiation exposure caused by prolonged procedure time[38] and a higher risk of contrast-induced nephropathy triggered by increased contrast load may further deteriorate patients' condition.[6] If patients in the immediate MV-PCI group were unable to tolerate the extremely prothrombotic and inflammatory milieu[39] and died early, they therefore did not survive long enough to develop MACE and revascularization in the long-term course. Correspondingly, the long-term risks of MACE and revascularization were lower in patients undergoing immediate MV-PCI than in those receiving CO-PCI. Based on our abovementioned discussion, investigating the short-term outcomes may provide more information about which one is better when considering immediate and staged MV-PCI. However, the short-term outcomes were unavailable in randomized trials. Therefore, we turned to real-world prospective observational studies for answers. Both short- and long-term follow-ups in prospective observational studies showed that immediate MV-PCI increased the risk of all-cause death when compared with staged MV-PCI. In addition, immediate MV-PCI paradoxically increased the risk of short-term all-cause death compared with CO-PCI, which seems contrary to the results from randomized trials. The randomized CULPRIT-SHOCK trial[40] was dedicated to comparing immediate MV-PCI *versus* CO-PCI in high-risk patients with STEMI and multivessel coronary artery disease complicated by cardiogenic shock. The results showed that at 30 days, the composite primary endpoint of all-cause death or renal-replacement therapy was

45.9% in the CO-PCI arm *versus* 55.4% in the immediate MV-PCI arm ($p = 0.01$). All-cause death was higher in immediate MV-PCI than in CO-PCI (51.6% *versus* 43.3%, $p = 0.03$). Therefore, in high-risk patients with STEMI and multivessel coronary artery disease complicated by cardiogenic shock, CO-PCI instead of immediate MV-PCI was advocated due to the reduced risk of short-term all-cause death. However, the rates of long-term (1-year) all-cause death (50.0% *versus* 56.9%; RR: 0.88; 95% CI: 0.76 to 1.01) and renal-replacement therapy (11.6% *versus* 16.4%; RR: 0.71; 95% CI: 0.49 to 1.03) were similar between CO-PCI *versus* immediate MV-PCI, yet rehospitalization for heart failure (5.2% *versus* 1.2%; RR: 4.46; 95% CI: 1.53 to 13.04) and revascularization (32.3% *versus* 9.4%; RR: 3.44; 95% CI, 2.39 to 4.95) occurred more frequently with CO-PCI.[38] Based on long-term results from the CULPRIT-SHOCK trial, we may wrongly conclude that immediate MV-PCI was superior to CO-PCI because of the reduced risks of rehospitalization for heart failure and revascularization. It is thought-provoking that during short-term follow-up, immediate MV-PCI increased the risk of all-cause death. Therefore, based on results from real-world prospective observational studies and the CULPRIT-SHOCK trial, a staged MV-PCI strategy may be the best option. Meanwhile, staged MV-PCI enables operators to have more time to appropriately evaluate the risks and benefits of additional revascularization, perhaps resulting in better patient selection[41] and avoiding the overestimation of stenosis severity in the acute phase of STEMI.[42] However, because of the deficiency of randomized trials comparing immediate and staged MV-PCI directly, the benefits of staged MV-PCI should be evaluated in future randomized trials. Two ongoing trials, MULTISTARS AMI (NCT03135275) and BioVasc (NCT03621501), which test the outcomes between immediate MV-PCI and staged MV-PCI, will help to further clarify the options of different MV-PCI strategies.

Another finding of our meta-analysis is the consistent benefit of MV-PCI guided by angiography or FFR. Meanwhile, two ongoing trials, FLOWER-MI (NCT02943954) and FRAME-AMI (NCT02715518), are comparing clinical outcomes following FFR-guided *versus* angiography-guided PCI in the treatment of non-IRA stenosis.

Our meta-analysis included studies from 2004 to 2019, and it is obvious that the use of DES increased with time in the included studies. Moreover, a study suggested that for STEMI patients receiving DES, a trend towards lower long-term mortality at 1 year was observed in comparison to the bare metal stent (BMS).[43] Therefore, meta-regression was performed to investigate whether the publication year and the percent of DES used may influence outcomes. However, the results indicated that publication year and DES did not exert effects on the association between the PCI strategy and clinical outcomes. In addition, during the past years, the recommendation for the PCI strategy for STEMI patients with multivessel coronary artery disease has changed oppositely. The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines did not recommend the MV-PCI strategy for STEMI patients with multivessel coronary artery disease (Class III, Level B), mainly based on observational studies.[44] In 2015, they upgraded the MV-PCI recommendation to Class IIb (Level B),[45] which was similar to the European Society of Cardiology/European Association of Cardiothoracic Surgery (ESC/EACTS) guideline in 2015.[46] With the publication of more well-designed randomized trials and meta-analyses, the latest 2017 ESC guideline has upgraded MV-PCI to Class IIa (Level A).[47] Therefore, recommendations are revised with the emergence of randomized trials and meta-analyses, and further randomized trials are needed to establish a solid conclusion on the optimal PCI strategy for STEMI patients with multivessel coronary artery disease.

Study limitations

First, the PRAGUE 13 trial has not yet been published, and we were unable to obtain the baseline characteristics. Meanwhile, the number of patients in the COMPLETE trial was large (4041, 53.0%); therefore, the results of our meta-analysis could have been skewed towards biases within the COMPLETE trial. However, sensitivity analyses performed by excluding these studies yielded similar results to the main analysis. Second, data are from different health care systems, different populations and different endpoint definitions, which might potentially increase the heterogeneity and impact the

outcomes. Moderate degrees of heterogeneity were observed in MACE, revascularization and heart failure in the pairwise meta-analysis. We attempted to mitigate this heterogeneity with several strategies, including using a random effects model and further subgroups of the MV-PCI strategy or the guidance of revascularization in our analysis. Third, although the included patients were all diagnosed with STEMI, yet the exclusion criteria were a little different, such as CTO, with some trials excluding CTO, yet others did not mention it. Finally, short-term outcomes were not reported in randomized trials and we were unable to evaluate the relative merits during short-term follow-up based on randomized trials.

Conclusion

Based on randomized trials, our findings demonstrated that MV-PCI in an immediate or staged procedure should be preferred for patients with STEMI and multivessel coronary artery disease compared with CO-PCI, which improved the long-term prognosis, but no data were reported on the short-term prognosis. As a supplement, the results in real-world patients derived from prospective observational studies suggested that staged MV-PCI was superior to immediate MV-PCI in the consideration of both short- and long-term all-cause death. Therefore, staged MV-PCI may be the optimal PCI strategy for patients with STEMI and multivessel coronary artery disease.

Author contributions
Meng-Jin Hu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing – original draft; Writing – review & editing.

Jiang-Shan Tan: Data curation; Formal analysis; Methodology; Software; Validation; Visualization; Writing – review & editing.

Wen-Yang Jiang: Data curation; Formal analysis; Investigation; Methodology; Software; Writing – review & editing.

Xiao-Jin Gao: Formal analysis; Methodology; Writing – review & editing.

Yue-Jin Yang: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Supervision; Validation; Writing – review & editing.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Supplemental material
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