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Optimal Timing of Complete Revascularization in Acute Coronary Syndrome: A Systematic Review and Meta-Analysis

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***Background*—**Studies have suggested that complete revascularization is superior to culprit-only revascularization for the treatment of enzyme-positive acute coronary syndrome. However, the optimal timing of complete revascularization remains unclear. We conducted a systematic review and meta-analysis of randomized controlled trials comparing single-stage complete revascularization with multistage percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction or non–ST-segment elevation myocardial infarction with multivessel disease.

***Methods and Results*—**We systematically searched the Cochrane Central Register of Controlled Trials, Embase, PubMed, and MEDLINE for randomized controlled trials comparing single-stage complete revascularization with multistage revascularization in patients with enzyme-positive acute coronary syndrome. The primary outcome was the incidence of major adverse cardiovascular events at longest follow-up. Data were pooled using DerSimonian and Laird random-effects models. Four randomized controlled trials (n=838) were included in our meta-analysis. The risk of unplanned repeat revascularization at longest follow-up was significantly lower in patients randomized to single-stage complete revascularization (risk ratio, 0.68; 95% CI, 0.47–0.99). Results also suggest a trend towards lower risks of major adverse cardiovascular events for patients randomized to single-stage revascularization at 6 months (risk ratio, 0.67; 95% CI, 0.40–1.11) and at longest follow-up (risk ratio, 0.79; 95% CI, 0.52–1.20). Risks of mortality and recurrent myocardial infarction at longest follow-up were also lower with single-stage revascularization, but 95% CIs were wide and included unity.

***Conclusions*—**Our results suggest that single-stage complete revascularization is safe. There also appears to be a trend towards lower long-term risks of mortality and major adverse cardiovascular events; however, additional randomized controlled trials are required to confirm the potential benefits of single-stage multivessel percutaneous coronary intervention. **(*J Am Heart Assoc*. 2017;6:e005381. DOI: 10.1161/JAHA.116.005381.)**

Key Words: acute coronary syndrome • complete revascularization • meta-analysis • percutaneous coronary intervention • single-stage revascularization • staged revascularization

Uncertainty has continuously revolved around the appropriate revascularization strategy for enzyme-positive acute coronary syndrome (ACS) patients (including ST-segment elevation myocardial infarction [STEMI] and non-STEMI [NSTEMI] patients) with multivessel disease (MVD). Previously, the debate was whether to conduct culprit-only or multivessel percutaneous coronary intervention (PCI). The 2011 American College of Cardiology/American Heart Association guidelines advised against single-stage complete revascularization in STEMI patients and recommended revascularization of nonculprit lesions at a later date only if clinically indicated.[1,2] However, several meta-analyses[3–17] have found multivessel revascularization to be superior to culprit-only revascularization for outcomes such as unplanned repeat revascularization,[9–12,15–17] all-cause mortality,[10] cardiac mortality,[10,16,17] and repeat infarction.[10,12,15]

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Accompanying Tables S1 through S6 and Figures S1 through S10 are available at http://jaha.ahajournals.org/content/6/4/e005381/DC1/embed/inline-supplementary-material-1.pdf

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Observational studies have also suggested that revascularization of nonculprit arteries in NSTEMI patients with MVD may be similarly beneficial.[18–24]

Consequently, American College of Cardiology/American Heart Association guidelines were revised in 2015 to issue a Class IIb recommendation (Level of Evidence B-R) with respect to multivessel PCI, which can be conducted either as a single-stage or multistage procedure in STEMI patients.[25] However, the guidelines provide no recommendation as to the optimal timing of multivessel PCI.[25,26] There is similar uncertainty regarding the optimal strategy for multivessel PCI in NSTEMI patients. The debate now is therefore whether complete revascularization should be conducted as a single-stage or a multistage procedure. The former involves the revascularization of all lesions during the index PCI of patients presenting with enzyme-positive ACS, whereas the latter consists of revascularization of the culprit lesion followed by revascularization of nonculprit lesions at a later date. The objective of this systematic review and meta-analysis was to compare the efficacy and safety of single-stage complete revascularization with those of staged multivessel PCI in enzyme-positive ACS patients with MVD.

Methods

Our systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[27] and followed a prespecified protocol. Searches of the Cochrane Central Register of Controlled Trials (CENTRAL), Embase (via Ovid), PubMed, and MEDLINE (via Ovid) databases were conducted in July 2016 using the following key words, medical subject headings (MeSH) terms, and Emtree terms: "PCI," "staged revascularization," "complete revascularization," "multi-vessel disease," and "myocardial infarction." A modified version of the McMaster RCT hedge[28] was used for each database to restrict the search to randomized controlled trials (RCTs) (full search strategies in Tables S1 through S4). Reference lists of selected studies and previous reviews were also manually searched for potentially eligible RCTs.

Study Selection

We included all RCTs conducted in enzyme-positive ACS patients with MVD that randomized participants to single-stage or multistage complete revascularization. Multistage revascularization was defined as initial revascularization of the culprit lesion only, followed by revascularization of ≥1 lesions as a planned procedure at a later date.

We excluded all abstracts and conference proceedings, observational studies, case reports, case series, commentaries, letters to the editor, editorials, reviews, and guidelines. We also excluded RCTs randomizing ≤50 participants, RCTs that did not report at least 1 outcome of interest (major adverse cardiovascular events [MACEs], all-cause mortality, cardiovascular mortality, myocardial infarction, and unplanned repeat revascularization), and basic science and animal models. Finally, inclusion was limited to English and French language publications.

Identified titles and abstracts were screened independently by 2 reviewers (R.G. and B.H.) according to the prespecified inclusion and exclusion criteria. Any publication deemed potentially relevant by either reviewer was carried forward to full-text review. Disagreements during full-text review were resolved by consensus or by a third reviewer (K.B.F.) when necessary.

Data Abstraction

Two abstracters (R.G. and B.H.) independently extracted data from eligible RCTs using a pilot-tested data collection spreadsheet. Discrepancies were resolved by consensus or, when necessary, by a third individual (K.B.F.). Collected data included trial name, year of publication, number of centers, sample size, maximum follow-up, number lost to follow-up, patient characteristics (age, sex, presence of cardiovascular risk factors), infarct location (anterior or inferior), extent of multivessel disease (2- or 3-vessel disease), procedural characteristics (number of treated lesions, number of stents per lesion, number of stents per patient, procedure duration, type of catheter-based therapy), pharmacological treatment characteristics (administration of antiplatelet agents, β-blockers, statins, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers), and the primary and secondary end points of interest (defined below).

End Points

The primary end point was the incidence of MACE at longest reported follow-up. MACE was defined as the composite of all-cause mortality, cardiovascular mortality, recurrent myocardial infarction, and the need for unplanned repeat revascularization (repeat PCI or coronary artery bypass grafting). Secondary outcomes of interest included the short-term incidence of MACEs, defined as MACEs occurring within 30 days or in-hospital, the incidence of MACEs at 6 months, and the incidences of the individual components of MACEs in the short term, at 6 months, and at longest follow-up. Tertiary end points included hemodynamic outcomes (technical success, hemodynamic stability before and after the intervention, left ventricular dysfunction presence and improvement, and periprocedural and postprocedural cardiac arrest), and safety outcomes (contrast-induced nephropathy,

volume of contrast administered, length of procedure, major bleeding, ischemic or hemorrhagic stroke, major bleeding, minor and major access site bleeding, hemoptysis, and intracranial bleeding).

Quality Assessment

The quality of included studies was evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[29] Trials were categorized as having a low, unclear, or high risk of bias among each of the following domains: adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Quality assessment was independently conducted by 2 reviewers (R.G. and B.H.), with disagreements resolved by consensus. All eligible RCTs were included in the meta-analysis regardless of their assessed quality.

Statistical Analysis

We used DerSimonian and Laird random-effects models with inverse variance weighting to estimate relative risks (RRs) and corresponding 95% CIs. Intention-to-treat analyses were used for all outcomes. Zero-event trials were included in our primary analysis through the use of a 0.5 continuity correction. Between-study heterogeneity was assessed using the I^2 statistic. In subgroup analyses, we stratified by STEMI versus NSTEMI. All analyses were performed using R version 3.2.2 (meta-package).

Results

Search Results

Our initial search yielded 4597 articles (Figure 1). One additional article was identified via hand search. After duplicates were removed, 2930 titles and abstracts were screened, of which 29 were retrieved for full-text review. Four RCTs (n=838) met the inclusion criteria of our systematic review and meta-analysis.[30–33]

Study Characteristics

Among the 4 RCTs, a total of 853 patients were randomized to single-stage complete revascularization or staged multivessel PCI. Three trials were restricted to STEMI patients with MVD presenting within 12 hours of symptom onset[31–33] (Table 1), while 1 trial was restricted to NSTEMI patients.[30] Sample sizes ranged from 89 to 542. Three trials excluded patients who presented with cardiogenic shock,[30–32] 3 trials excluded patients with left main coronary disease,[31–33] and 2 trials excluded patients with previous coronary artery bypass grafting.[30,31]

Follow-up was 6 months for 2 of the included trials,[32,33] 12 months for 1 trial,[30] and a mean 2.5±1.4 years for 1 trial[31] (Table 1). Trials reported a varying combination of 30-day clinical events,[30,31] 6-month clinical events,[30,32,33] and 12-month clinical events.[30] Follow-up was complete in 2 trials.[30,31] Fifteen patients were lost to follow-up in 1 trial,[32] and the number of patients lost to follow-up was not reported in 1 trial.[33]

Baseline Patient, Procedural, and Pharmacological Characteristics

Patient, procedural, and pharmacological characteristics were similar among trials and between treatment arms (Table 2). Men represented between 36% and 40% of trial participants, and the mean ages ranged from 58.6 to 73 years. The rates of previous myocardial infarction ranged from 4.7% to 29.2% and appeared to be similar between treatment groups.[30,32,33] Left ventricular ejection fraction values ranged from 41.6% to 52.2%. Among trials reporting the number of anterior infarcts, there appeared to be no significant differences between treatment groups or treatment arms. Cardiovascular risk factors were similarly balanced between treatment arms.

The mean number of treated vessels per patient was similar among both trials[30,32] that reported it and between treatment arms (≈2.3 vessels) (Table 3). The mean number of stents per patient varied from 0.85 to 3 and was similar between treatment groups.[30,32,33] The mean length of time between procedures in the multistage arm varied from 4.76 to 58.6 days. In all 4 trials, staged revascularization was conducted in a single procedure apart from index PCI. When reported, procedure time and volume of contrast used varied among trials. Tarasov et al[33] used only zotarolimus-eluting stents in their revascularization strategies, whereas the Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention (SMILE) trial[30] and Politi et al[31] used both drug-eluting stents and bare metal stents. Ochala et al[32] did not report on characteristics of implanted stents.

Pharmacological therapies administered postprocedure were similar among trials (Table 3). The proportions of patients taking aspirin[30,31,33] and P2Y12 receptor inhibitors (clopidogrel, ticagrelor, prasugrel)[30–32] was 96.8% to 100%, β-blockers was 82.5% to 93.6%,[30,31] and statins at discharge was 90.5% to 100%.[30,31,33] The proportion of patients taking GPIIb/IIIa inhibitors ranged between 12.9% and 57.0%,[30,32] while that of patients taking angiotensin-converting enzyme inhibitors/angiotensin receptor blockers ranged from 55.6% to 97.0%.[30,31] In all trials, administration of pharmacological therapies was similar between treatment groups.

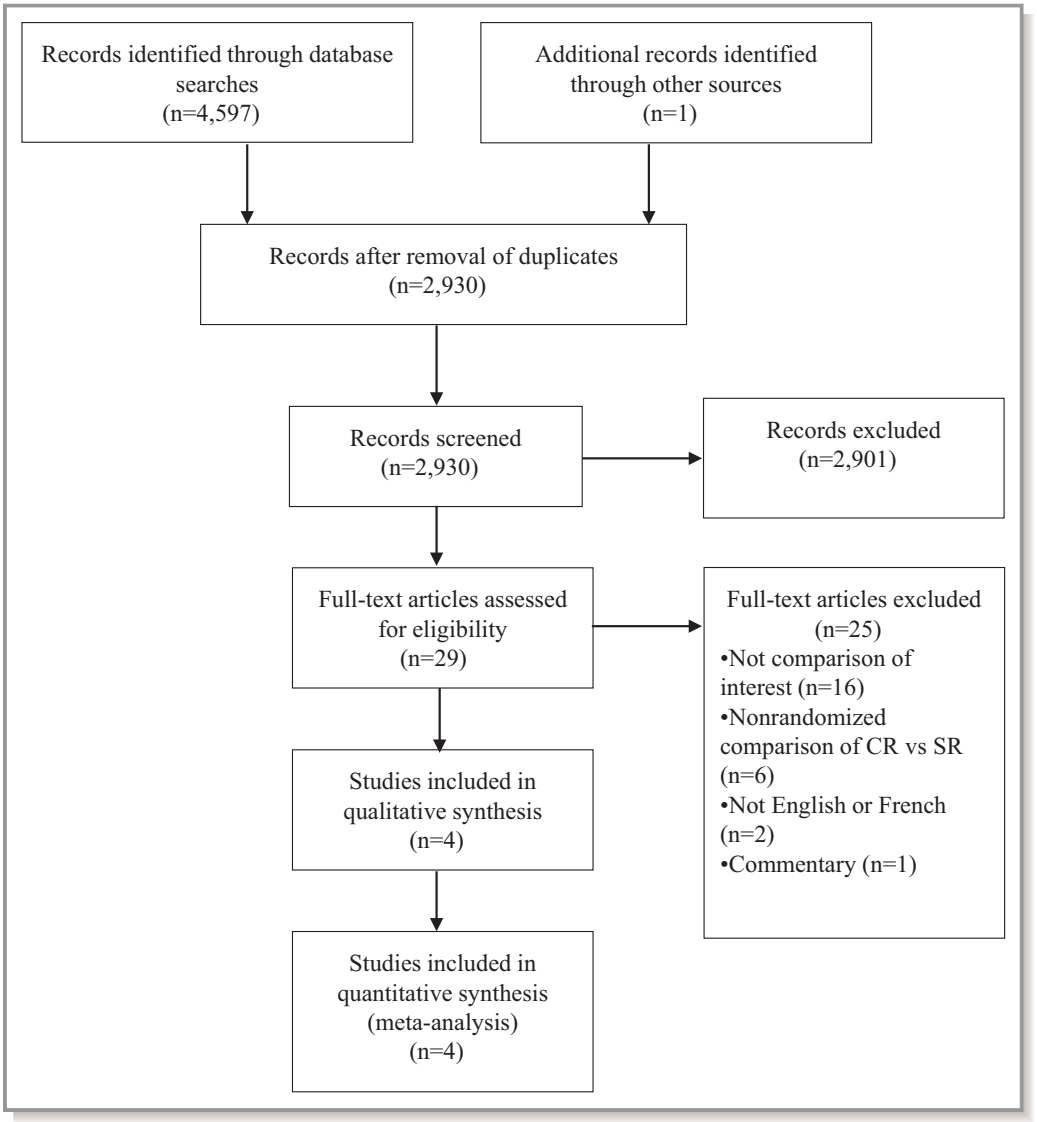

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. CR indicates culprit-only revascularization; SR, staged revascularization.

Quality Assessment

There was a low or unclear risk of bias among the various domains assessed using the Cochrane Collaboration's risk of bias tool[29] (Table S5). None of the trials discussed allocation concealment and therefore had an unclear risk of bias in this domain. Sequence generation in Politi et al[31] was adequately described and deemed to have a low risk of bias, but was not described in the remaining RCTs. All trials had an open-label design, as blinding of patients and personnel to treatment allocation was not feasible. However, the SMILE trial[30] used a blinded independent end point committee to adjudicate outcomes and the trial was therefore judged to have a low risk of bias in the domain of blinding. The remaining trials had an unclear risk of bias in this domain. Politi et al[31] and the Primary Percutaneous Intervention for Acute Myocardial Infarction (PRIMA) trial[32] had a low risk of bias for incomplete outcome data as follow-up was complete. Tarasov et al[33] and SMILE[30] had an unclear risk of bias as the numbers lost to follow-up and the reasons for losses to follow-up were not reported, respectively.

Long-Term Clinical Events

When data were pooled among trials, the risk of the composite outcome MACE in the single-stage complete revascularization treatment arm was consistently lower than that in the multistage PCI arm at 6 months (RR, 0.67; 95% CI, 0.40–1.11) (Figure 2) and at longest follow-up (RR, 0.79; 95% CI, 0.52–1.20) but did not reach statistical significance

Table 1. Characteristics of RCTs Comparing SS With MS in Patients With Acute Coronary Syndrome

Trial	Publication Year	Multicenter	Sample Size	No. (ITT)		Study Population	Maximum Follow-Up, mo	Losses to Follow-Up, %	
				SS	MS			SS	MS
Sardella et al (SMILE)[30]	2015	No	542	264	263	NSTEMI	12	2.2	3.3
Politi et al[31]	2009	No	130*	65	65	STEMI	NR†	0	0
Ochala et al (PRIMA)[32]	2009	Yes	92	48	44	STEMI	6	0	0
Tarasov et al[33]	2014	Yes	89	46	43	STEMI	6	NR	NR

ITT indicates intention to treat; MS, multistage revascularization; NR, not reported; NSTEMI, non–ST-segment elevation myocardial infarction; PRIMA, the Primary Percutaneous Intervention for Acute Myocardial Infarction trial; RCTs, randomized controlled trials; SMILE, Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention trial; STEMI, ST-segment elevation myocardial infarction; SS, single-stage complete revascularization.
*This was a 3-arm trial. A total of 130 participants were randomized between SS and MS. A total of 218 were randomized to the trial between SS, MS, and culprit-only revascularization.
†The authors reported a mean follow-up of 2.5±1.4 years.

(Figure 3). The observed trends appear to be driven by a significant decrease in the risk of unplanned repeat revascularization among patients randomized to single-stage revascularization (RR, 0.68; 95% CI, 0.47–0.99) (Figure 3). In addition, results suggest a potential benefit of single-stage complete revascularization over multistage PCI for all-cause mortality at 6 months (RR, 0.50; 95% CI, 0.25–1.01) (Figure 2) and at longest follow-up (RR, 0.68; 95% CI, 0.41–1.14) (Figure 3), although 95% CIs were wide and included unity. Finally, although results for the remaining individual end points were inconclusive due to wide 95% CIs, all were numerically lower with single-stage compared with multistage complete revascularization.

Short-Term Clinical Events

Numerical increases in short-term mortality in the single-stage compared with the multistage complete revascularization arm were observed in 2 trials (Table S6). The SMILE trial reported 6 deaths in the single-stage arm (2.27%) and 2 deaths in the multistage arm (0.76%)[30] at 1 month (P=0.28), while Politi et al[31] reported 2 in-hospital deaths in the single-stage arm (3.08%) and none in the multistage arm. However, lack of data from other trials prevented the pooling of data among trials, rendering the evidence inconclusive for this outcome.

The SMILE trial reported no cases of contrast-induced nephropathy,[30] while Politi et al[31] reported 1 case in the single-stage arm (1.54%) and 2 (3.08%) in the multistage arm (Table S6). Meta-analysis was not feasible for this outcome because of the low number of events and lack of data from other trials.

Subgroup Analyses

Subgroup analyses were performed by infarct type (STEMI or NSTEMI) (Figures S1 through 10). The protective effect of single-stage revascularization against the primary end point MACE at longest follow-up was significant among NSTEMI patients (RR, 0.59; 95% CI, 0.40–0.86) and remained inconclusive among STEMI patients (RR, 1.01; 95% CI, 0.63–1.63) (Figure S2). Similarly, the protective effect of single-stage revascularization against unplanned repeat revascularization was maintained in NSTEMI patients at longest follow-up (RR, 0.55; 95% CI, 0.34–0.90), but was inconclusive in STEMI patients due to wide 95% CIs (RR, 0.91; 95% CI, 0.51–1.62) (Figure S10). However, data on NSTEMI patients were only available from a single trial, thus limiting the conclusions that could be drawn.

Discussion

Our study was designed to determine the optimal timing of complete revascularization strategies in enzyme-positive ACS patients with multivessel disease, by comparing single-stage complete revascularization with multivessel PCI conducted as a staged procedure. We found that single-stage complete revascularization was associated with significantly decreased rates of unplanned repeat revascularization at longest follow-up compared with staged multivessel PCI. Our results also suggest that single-stage complete revascularization may have a protective effect against MACEs at longest follow-up, but with only 4 trials with modest sample sizes, the pooled sample size was not sufficient to provide definitive results. Our results also revealed a trend towards a possible protective effect of single-stage complete revascularization against all-cause mortality at 6 months and at longest follow-up. However, this observed decrease appears to have been driven by the results of the SMILE trial[30] and does not parallel a reduction in long-term cardiovascular death, highlighting the need for further RCTs. Overall, our results suggest that single-stage complete revascularization is safe and might have a

Table 2. Baseline Characteristics of Patients Randomized to SS or MS

Trial	Men, %		Age*		Previous MI, %		LVEF*		Anterior Infarct, %		HTN, %		DM, %		Smoker, %		DLP, %	
	SS	MS	SS	MS	SS	MS	SS	MS	SS	MS	SS	MS	SS	MS	SS	MS	SS	MS
Sardella et al (SMILE)[30]	39	40	72 (61–78)†	73 (62–78)†	26.9	23.6	50 (40–55)†	50 (40–55)†	NR	NR	73.1	66.2	37.1	39.5	45.4	40.7	57.6	54.4
Politi et al[31]	38	40	64.5 (11.7)	64.1 (11.1)	NR	NR	45.4 (10.4)	45.9 (8.6)	47.7	43.1	49.2	64.6	13.5	18.5	NR	NR	NR	NR
Ochala et al (PRIMA)[32]	38	36	65 (8.3)	67 (7.9)	29.2	22.7	41.6 (4.3)	44.7 (NR)	45.8	45.4	52.1	47.7	34.1	32.6	37.5	43.2	81.3	90.9
Tarasov et al[33]	36	39	58.6 (11)	58.9 (10.4)	10.8	4.7	51 (9)	52.2 (7.4)	45.7	30.2	95.7	86.0	26.1	20.9	NR	NR	NR	NR

DLP indicates dyslipidemia; DM, diabetes mellitus; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MS, multistage revascularization; NR, not reported; PRIMA, the Primary Percutaneous Intervention for Acute Myocardial Infarction trial; SBP, systolic blood pressure; SMILE, the Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention trial; SS, single-stage complete revascularization.

*Data are reported as mean (SD) unless otherwise stated.

†Data are reported as median (interquartile range).

favorable efficacy profile regarding MACEs in the long term compared with multistage revascularization. However, large, high-quality RCTs are needed to conclusively determine whether single-stage complete revascularization is more efficacious and safer than multistage PCI.

The results of our meta-analysis conflict with those recently published by Li et al,[34] who found that multistage PCI significantly reduced short-term and long-term mortality compared with single-stage multivessel PCI. Their meta-analysis, however, pooled data from both RCTs and observational studies. Given the inherent presence of confounding and other bias in observational studies, the results of their meta-analysis should be interpreted with caution. Furthermore, in analyses restricted to RCTs, the authors used nonrandomized data from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) RCT, which was assigned a substantial weight in their meta-analysis. Their results were therefore driven by these observational data, which explains the discrepancy between their results and our own. Our results also conflict with those of the network meta-analysis conducted by Bajaj et al,[35] which was restricted to RCTs conducted in STEMI patients and compared culprit-only revascularization, single-stage complete revascularization, and multistage PCI. Their results showed that the risk of MACEs did not differ between the 2 arms. However, their small sample size (3 trials, 311 patients) resulted in imprecise estimates, underscoring the need to reassess this issue in light of the recently published SMILE trial.[30] In addition, our results conflict with those of Vlaar et al,[5] who found that multistage PCI was associated with lower short-term and long-term mortality compared with single-stage complete revascularization. However, their meta-analysis was not restricted to RCTs and the analysis included data from only 2 RCTs (n=222). When restricted to the 2 RCTs, their analysis was inconclusive due to very wide 95% CIs.

In other meta-analyses[3,4] that compared culprit-only with multivessel revascularization, subgroup analyses were also performed to compare single-stage versus multistage approaches to multivessel revascularization. The results of those analyses were inconsistent. In their 2014 meta-analysis, Bainey et al[3] found that when compared with culprit-only revascularization, staged multivessel PCI had a greater long-term survival benefit than single-stage complete revascularization. However, the 2016 meta-analysis by Bainey et al,[4] restricted to RCTs, found no difference between multistage PCI and culprit-only revascularization regarding long-term survival, whereas a trend toward long-term survival was observed in patients undergoing single-stage complete revascularization compared with culprit-only revascularization. These conflicting results are likely due to the lack of randomization of participants between the 2 multivessel

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Table 3. Procedural and Pharmacological Characteristics of Patients Randomized to SS or MS

Trial	Vessels Treated Per Patient*		Stents Per Patient*		Procedure Time, min*		Time Between Procedures in the MS Arm, d*	Volume of Contrast Used*		Therapy at Discharge							
										ASA, %		Clopidogrel Prasugrel Ticagrelor, %		GPI, %		ACEI or ARB, %	
	SS	MS	SS	MS	SS	MS		SS	MS	SS	MS	SS	MS	SS	MS	SS	MS
Sardella et al (SMILE)[30]	2.4 (0.5)	2.3 (0.8)	3.0 (2.0–4.0)†	3.0 (2.0–4.0)†	61 (38–79)†	44 (28–59)†	4.8 (1.2)	295 (195–400)†	180 (140–230)†	98.9‡	98.5‡	100	100	12.9	14.1	97.0	94.7
Politi et al[31]	NR	NR	NR	NR	NR	NR	58.6 (12.9)	NR	NR	98.4	100	96.8	100	NR	NR	55.6	58.5
Ochala et al (PRIMA)[32]	2.3 (0.4)	2.3 (0.4)	1.0 (0.2)	0.9 (0.3)	65.8 (13.3)	84.1 (14.7)	27.3 (12.8)	315.6 (4)	243.9 (8)	NR	NR	100	100	57.0	50.9	NR	NR
Tarasov et al[33]	NR	NR	2.6 (0.8)	2.6 (0.9)	NR	NR	8.5 (4.2)	313.8 (101.5)	353.6 (167.6)	100	100	NR	NR	NR	NR	NR	NR

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; GPI, glycoprotein IIb/IIIa inhibitors; MS, multistage revascularization; NR, not reported; PRIMA, the Primary Percutaneous Intervention for Acute Myocardial Infarction trial; SMILE, the Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention trial; SS, single-stage complete revascularization.

*Data are reported as mean (SD) unless otherwise stated.

†Data are reported as median (interquartile range).

‡Defined in this study as preprocedural and postprocedural therapy.

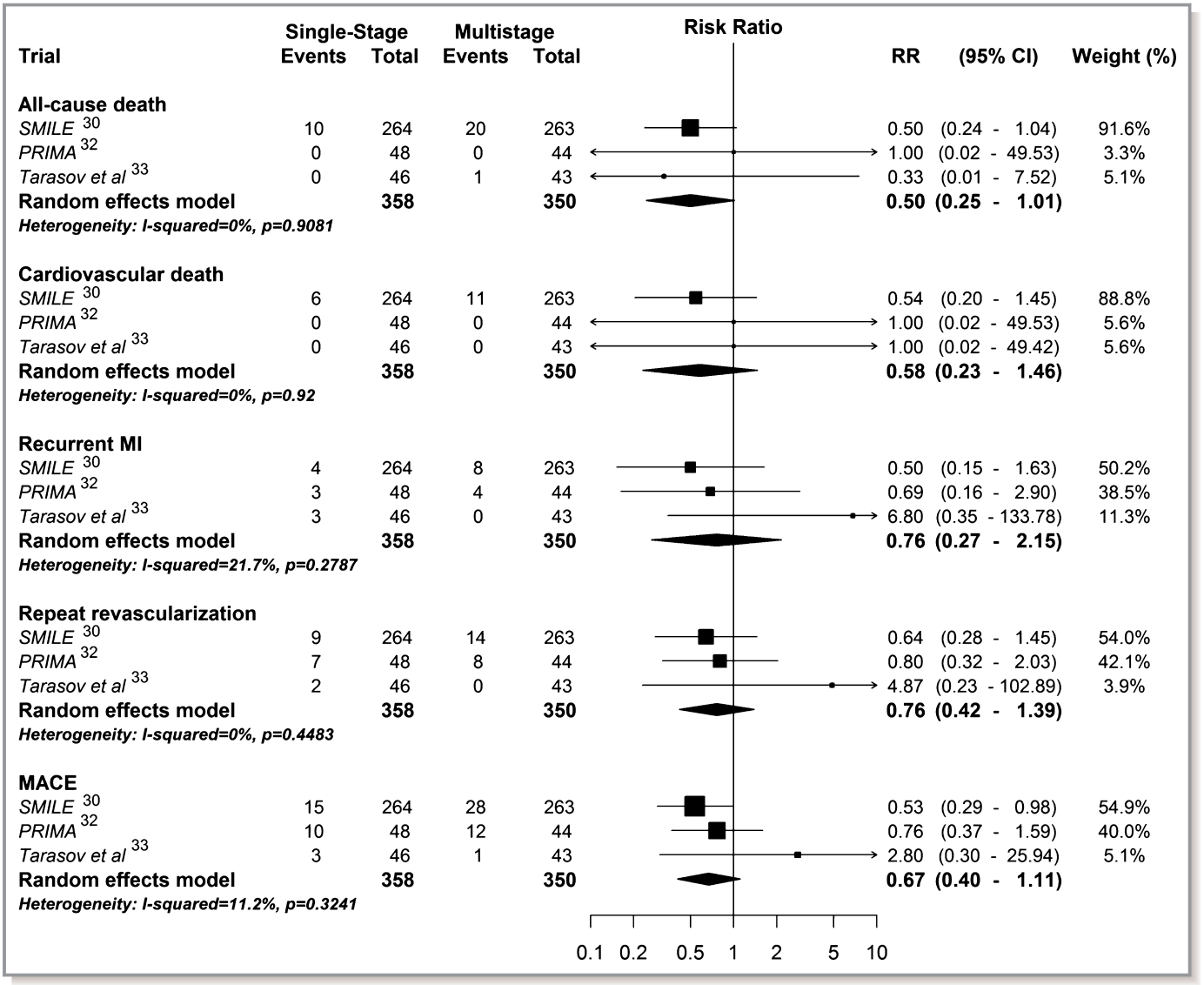

Figure 2. Forest plots of the relative risks of adverse cardiovascular events at 6 months from randomized controlled trials comparing single-stage with multistage complete revascularization. MACE indicates major adverse cardiovascular event; MI, myocardial infarction; PRIMA, the Primary Percutaneous Intervention for Acute Myocardial Infarction trial; RR, risk ratio; SMILE, Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention trial.

revascularization strategies and their indirect comparison through the common comparator culprit-only revascularization.

With regards to short-term mortality, Bainey et al[3] found that single-stage and multistage complete revascularization were associated with higher and lower in-hospital mortality compared with culprit-only revascularization, respectively. These results are consistent with our own findings, which found numerically higher rates of in-hospital mortality associated with single-stage multivessel PCI. However, pooling of short-term mortality data was not possible in our study because of limited number of trials and limited reporting of these events. In addition, the analyses in previous studies were indirect and nonrandomized and thus subject to biases such as confounding. As such, further RCTs reporting short-term clinical events are needed in order to compare the short-term efficacy and safety of single-stage complete revascularization with those of multistage PCI.

With single-stage complete revascularization come risks associated with longer procedure times and larger contrast volumes, such as increased rates of contrast-induced nephropathy, procedural complications, in-hospital mortality, and stent thrombosis.[25,36,37] However, there are several known advantages of conducting multivessel revascularization in a single setting. The PRIMA trial[32] found that single-stage complete revascularization resulted in significantly greater left ventricular ejection fraction compared with multistage revascularization in STEMI patients after 30 days. Furthermore,

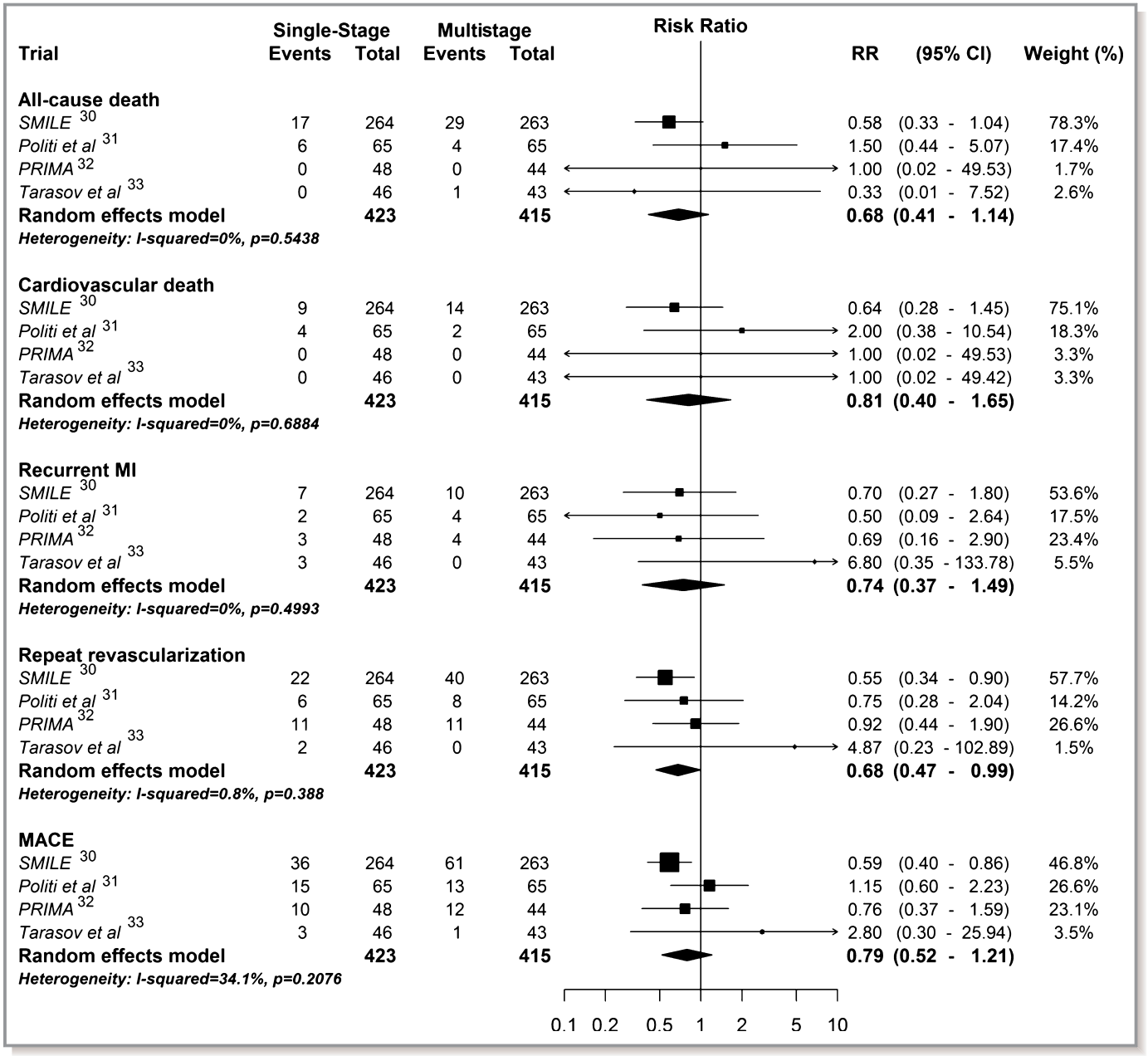

Figure 3. Forest plots of the relative risks of adverse cardiovascular events at longest follow-up from randomized controlled trials comparing single-stage with multistage complete revascularization. MACE indicates major adverse cardiovascular event; MI, myocardial infarction; PRIMA, the Primary Percutaneous Intervention for Acute Myocardial Infarction trial; RR, risk ratio; SMILE, Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention trial.

conducting multivessel PCI in a single procedure has the potential to limit hospitalization days and lower medical costs. Additional RCTs are needed in order to conclusively determine which revascularization strategy is more efficacious and safer.

Study Limitations

Our meta-analysis has several potential limitations. First, despite pooling clinical events among the 4 trials, 95% CIs were still wide. Consequently, although our results suggest that single-stage revascularization has beneficial effects on cardiovascular events, additional, larger RCTs comparing single-stage with multistage revascularization are needed before definitive conclusions can be drawn. Second, our pooled analyses were restricted to long-term outcomes, as short-term outcomes and safety outcomes were rarely and inconsistently reported among trials. Third, 3 RCTs were conducted in STEMI patients while only 1 RCT was conducted in NSTEMI patients. The results of our meta-analysis were largely driven by the single NSTEMI trial, which had a sample

size of 542 compared with the total sample size of 311 patients from the 3 STEMI trials. Analyses stratified by STEMI/NSTEMI status also suggest that our meta-analysis was underpowered to make conclusions regarding the comparative efficacy of single-stage versus multistage complete revascularization in STEMI patients with multivessel disease. This further highlights the need for additional large RCTs that compare these two revascularization options in diverse patient populations. Finally, there was some heterogeneity between studies in study population, procedural characteristics, outcome definition, and length of follow-up. However, random-effects models were used in our meta-analysis, which account for between-study heterogeneity, and the I^2 was low for all analyses.

Conclusions

Our meta-analysis was designed to compare the efficacy and safety of single-stage complete revascularization with those of multistage revascularization in enzyme-positive ACS patients with MVD. The risk of unplanned repeat revascularization was found to be significantly lower in patients randomized to single-stage compared with multistage revascularization at longest follow-up. Our analysis also indicates a trend towards lower risks of mortality and MACEs in the long term with single-stage complete revascularization as compared with a multistage procedure. Overall, results show promise for single-stage revascularization; however, additional, larger RCTs are required to confirm its benefits.

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Disclosures

None.

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Optimal Timing of Complete Revascularization in Acute Coronary Syndrome: A Systematic Review and Meta-Analysis

Supplemental Material

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Table S1. PubMed search strategy for randomized controlled trials comparing single-stage to multi-stage complete revascularization.

Search Number	Description	Number of Publications
1	((percutaneous coronary[MeSH Terms]) OR (stents[MeSH Terms]) OR (balloon dilatation [MeSH Terms]) OR (Myocardial revascularization [MeSH Terms]) OR (angioplast* [Title/abstract]) OR ((percutaneous[Title/abstract]) AND (coronary[Title/abstract]) AND (intervention[Title/abstract])) OR ((percutaneous[Title/abstract]) AND (coronary[Title/abstract]) AND (revascularization[Title/abstract])) OR ((percutaneous[Title/abstract]) AND (coronary[Title/abstract]) AND (revascularisation[Title/abstract])) OR (revascularization*[Title/abstract]) OR (revascularisation*[Title/abstract]) OR (reperfusion*[Title/abstract]) OR (stent*[Title/abstract]) OR (balloon*[Title/abstract]) OR (dilatat*[Title/abstract]) OR (transluminal*[Title/abstract]) OR ((coronary[Title/abstract]) AND atherectom*[Title/abstract]))	345,406
2	(Staged[Title/abstract])	17,986
3	(((multivessel[Title/abstract]) OR (multi vessel[Title/abstract]) OR (multi-vessel[Title/abstract])) AND ((revascularization*[Title/abstract]) or (revascularization*[Title/abstract]))) OR ((complete[Title/abstract]) AND ((revascularization*[Title/abstract]) or (revascularization*[Title/abstract])))	4,527
4	(((non culprit[Title/abstract]) OR (non-culprit[Title/abstract]) OR (non-infarct[Title/abstract]) OR (non infarct[Title/abstract]) OR (non-infarct-related[Title/abstract]) OR (non infarct-related[Title/abstract])) AND ((artery[Title/abstract]) OR (arteries[Title/abstract]) OR (vessel*[Title/abstract]) OR (lesion*[Title/abstract]) OR (reperfusion*[Title/abstract]) OR (revascularization* [Title/abstract]) OR (revascularisation*[Title/abstract])))	385
5	(myocardial infarction [MeSH Terms]) OR ((acute[Title/abstract]) AND (coronary[Title/abstract]) AND (syndrome[Title/abstract])) OR (((myocard*[Title/abstract]) OR (heart[Title/abstract])) AND (infarct*[Title/abstract])) OR (STEMI[Title/abstract]) OR (((ST-elevation[Title/abstract]) OR (ST elevation[Title/abstract]) OR (ST-segment-elevation[Title/abstract]) OR (ST segment-elevation[Title/abstract]) OR (ST-segment elevation[Title/abstract]) OR (ST segment elevation[Title/abstract])) AND (infarct*[Title/abstract])) OR (NSTEMI[Title/abstract]) OR (((Non-ST-elevation[Title/abstract]) OR (Non ST elevation[Title/abstract]) OR (Non-ST elevation[Title/abstract]) OR (Non ST-elevation[Title/abstract]) OR (Non ST-segment-elevation[Title/abstract]) OR (Non ST segment-elevation[Title/abstract]) OR (Non ST-segment elevation[Title/abstract]) OR (Non ST segment elevation[Title/abstract]) OR (Non-ST-segment-elevation[Title/abstract]) OR (Non-ST-segment elevation[Title/abstract]) OR (Non-ST segment elevation[Title/abstract])) AND (infarct*[Title/abstract]))	232,404
6	((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab] OR randomised[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])	3,328,338
7	1 AND (2 OR 3 OR 4) AND 5 AND 6	1,029

Table S2. CENTRAL search strategy for randomized controlled trials comparing single-stage to multi-stage complete revascularization

Search Number	Description	Number of Publications
1	(MeSH descriptor: [Angioplasty] explode all trees) OR (MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees) OR (MeSH descriptor: [Stents] explode all trees) OR (MeSH descriptor: [Dilatation] explode all trees) OR (MeSH descriptor: [Myocardial Revascularization] explode all trees) OR (angioplast*:ti,ab,kw) OR ((percutaneous*:ti,ab,kw) AND (coronary*:ti,ab,kw) AND (intervention*:ti,ab,kw)) OR ((percutaneous*:ti,ab,kw) AND (coronary*:ti,ab,kw) AND (revascularization*:ti,ab,kw)) OR ((percutaneous*:ti,ab,kw) AND (coronary*:ti,ab,kw) AND (revascularisation*:ti,ab,kw)) OR (revascularization*:ti,ab,kw) OR (revascularisation*:ti,ab,kw) OR (reperfusion*:ti,ab,kw) OR (stent*:ti,ab,kw) OR (balloon*:ti,ab,kw) OR (dilatat*:ti,ab,kw) OR (transluminal*:ti,ab,kw) OR ((coronary*:ti,ab,kw) AND atherectom*:ti,ab,kw))	28,333
2	(staged*:ti,ab,kw)	925
3	(((multivessel*:ti,ab,kw) OR (multi vessel*:ti,ab,kw) OR (multi-vessel*:ti,ab,kw)) AND ((revascularization*:ti,ab,kw) OR (revascularisation*:ti,ab,kw)))) OR ((complete*:ti,ab,kw) AND ((revascularization*:ti,ab,kw) OR (revascularisation*:ti,ab,kw)))	1,037
4	((((non culprit)*:ti,ab,kw) OR ((non-culprit)*:ti,ab,kw) OR ((non-infarct)*:ti,ab,kw) OR ((non infarct)*:ti,ab,kw) OR ((non-infarct-related)*:ti,ab,kw) OR ((non infarct-related)*:ti,ab,kw))) AND ((arter*:ti,ab,kw) OR (vessel*:ti,ab,kw) OR (lesion*:ti,ab,kw) OR (reperfusion*:ti,ab,kw) OR (revascularization*:ti,ab,kw) OR (revascularisation*:ti,ab,kw)))	1,035
5	(MeSH descriptor: [myocardial infarction] explode all trees) OR ((acute*:ti,ab,kw) AND (coronary*:ti,ab,kw) AND (syndrome*:ti,ab,kw)) OR (((myocard*:ti,ab,kw) OR (heart*:ti,ab,kw)) AND (infarct*:ti,ab,kw)) OR (STEMI*:ti,ab,kw) OR ((((ST-elevation)*:ti,ab,kw) OR ((ST elevation)*:ti,ab,kw) OR ((ST-segment-elevation)*:ti,ab,kw) OR ((ST segment-elevation)*:ti,ab,kw) OR ((ST-segment elevation)*:ti,ab,kw) OR ((ST segment elevation) *:ti,ab,kw)) AND (infarct*:ti,ab,kw)) OR (NSTEMI*:ti,ab,kw) OR ((((Non-ST-elevation)*:ti,ab,kw) OR ((Non ST elevation)*:ti,ab,kw) OR ((Non-ST elevation) *:ti,ab,kw) OR ((Non ST-elevation)*:ti,ab,kw) OR ((Non ST-segment-elevation)*:ti,ab,kw) OR ((Non ST segment-elevation)*:ti,ab,kw) OR ((Non ST-segment elevation)*:ti,ab,kw) OR ((Non ST segment elevation)*:ti,ab,kw) OR ((Non-ST-segment-elevation)*:ti,ab,kw) OR ((Non-ST-segment elevation)*:ti,ab,kw) OR ((Non-ST segment elevation) *:ti,ab,kw)) AND (infarct*:ti,ab,kw))	22,588
6	1 AND (2 OR 3 OR 4) AND 5	1,119

Table S3. Ovid EMBASE search strategy for randomized controlled trials comparing single-stage to multi-stage complete revascularization

Search Number	Description	Number of Publications
1	(exp angioplasty/) or (angioplasty.mp) or (exp percutaneous coronary intervention/) or ((percutaneous and coronary and intervention).mp) or ((percutaneous and coronary and stent).mp) or (exp stents/) or (stent*.mp) or ((stent and assisted and angioplasty).mp) or ((stent and balloon).mp) or (stent and balloon expansion).mp or (stent and balloon and inflation).mp or (exp percutaneous transluminal angioplasty/) or ((percutaneous and transluminal and angioplasty).mp) or (exp percutaneous transluminal angioplasty balloon/) or ((percutaneous and transluminal and angioplasty and balloon).mp) or ((percutaneous and transluminal and stent and angioplasty).mp) or ((percutaneous and transluminal and stenting and angioplasty).mp) or (exp ballon/) or (balloon.mp) or (exp angioplasty/ and stenting/) or ((balloon and angioplasty and stenting).mp) or ((balloon and angioplasty and catheter).mp) or (exp dilatation/) or (dilatation.mp) or (exp coronary atherectomy/) or ((coronary and atherectomy).mp) or ((percutaneous and coronary and revascularization).mp) or (percutaneous and coronary and rotational and ablation).mp or ((percutaneous and coronary and thrombectomy).mp) or ((percutaneous and cutting and balloon and angioplasty).mp) or ((coronary and angioplasty).mp) or (exp coronary angioplasty/) or (exp percutaneous transluminal coronary angioplasty/) or ((percutaneous and transluminal and coronary and angioplasty).mp) or (transluminal.mp) or ((percutaneous and cutting and balloon and incision and dilatation).mp)	324,967
2	(staged.mp) or (stage*.mp) or ((stage* and revascularization).mp) or ((stage* and revascularisation).mp)	892,402
3	((multivessel and revascularization).mp) or ((multivessel and revascularisation).mp) or ((multi and vessel and revascularization).mp) or ((multi and vessel and revascularisation).mp) or ((multi-vessel and revascularization).mp) or ((multi-vessel and revascularisation).mp)	3,954
4	((non and culprit and coronary and artery).mp) or ((non and culprit and coronary and lesion).mp) or ((non and culprit and lesion).mp) or ((non and culprit).mp) or ((non-culprit and artery).mp) or ((non and culprit and artery).mp) or ((non and culprit and vessel).mp) or ((non-culprit and vessel).mp) or ((non-culprit and lesion).mp) or ((non-infarct-related and artery).mp) or ((non and infarct and related and artery).mp) or ((non and infarct and related and lesion).mp) or ((non-infarct-related and lesion).mp) or ((non-infarct and artery and revascularization).mp) or ((non-infarct and artery and revascularisation).mp) or ((non and infarct and artery and revascularization).mp) or ((non and infarct and artery and revascularisation).mp) or ((non and infarct and revascularization).mp) or ((non and infarct and revascularisation).mp) or ((non and culprit and revascularization).mp)	3,913
5	(exp myocardial infarction/) or ((myocardial and infarction).mp) or ((heart and infarction).mp) or (exp acute coronary syndrome/) or ((acute and coronary and syndrome).mp) or (exp heart infarction/) or (exp ST elevation myocardial infarction/) or ((STEMI).mp) or ((ST and elevation and myocardial and infarction).mp) or ((ST-elevation and myocardial and infarction).mp) or ((((ST-elevation).mp) or ((ST and elevation).mp) or ((ST-segment-elevation).mp) or ((ST-segment and elevation).mp) or ((ST and segment-elevation).mp) or ((ST and segment and elevation).mp)) AND (((infarct*).mp))) or (exp non ST segment elevation myocardial infarction/) or ((non and ST and elevation and myocardial and infarction).mp) or ((NSTEMI).mp) or ((((non and ST-elevation).mp) or ((non-ST-elevation).mp) or ((non-ST and elevation).mp) or ((non and ST and elevation).mp) or ((non-ST-segment-elevation).mp) or ((non and ST-segment-elevation).mp) or	299,228

	((non-ST-segment and elevation).mp) or ((non and ST-segment and elevation).mp) or ((non-ST and segment-elevation).mp) or ((non and ST and segment-elevation).mp) or ((non and ST and segment and elevation).mp)) AND (((infarct*).mp)))	
6	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.	1,449,826
7	1 AND (2 OR 3 OR 4) AND 5 AND 6	1,071

Table S4. Ovid MEDLINE search strategy for randomized controlled trials comparing single-stage to multi-stage complete revascularization

Search Number	Description	Number of Publications
1	(exp angioplasty/) or (angioplasty.mp) or (exp percutaneous coronary intervention/) or ((percutaneous and coronary and intervention).mp) or (exp stents/) or (stent*.mp) or (exp angioplasty, balloon, coronary/) or ((stent and assisted and angioplasty).mp) or ((stent and balloon).mp) or (stent and balloon expansion).mp or (stent and balloon and inflation).mp or ((percutaneous and transluminal and angioplasty).mp) or ((percutaneous and transluminal and angioplasty and balloon).mp) or ((percutaneous and transluminal and stent and angioplasty).mp) or ((percutaneous and transluminal and stenting and angioplasty).mp) or (balloon.mp) or ((balloon and angioplasty and stenting).mp) or ((balloon and angioplasty and catheter).mp) or (exp dilatation/) or (dilatation.mp) or (exp atherectomy, coronary/) or ((coronary and atherectomy).mp) or ((percutaneous and coronary and revascularization).mp) or (percutaneous and coronary and rotational and ablation).mp or ((percutaneous and coronary and thrombectomy).mp) or ((percutaneous and cutting and balloon and angioplasty).mp) or ((coronary and angioplasty).mp) or (exp coronary angioplasty/) or (exp percutaneous transluminal coronary angioplasty/) or ((percutaneous and transluminal and coronary and angioplasty).mp) or (transluminal.mp) or ((percutaneous and cutting and balloon and incision and dilatation).mp)	176,756
2	(staged.mp) or (stage*.mp) or ((stage* and revascularization).mp) or ((stage* and revascularisation).mp)	645,006
3	((multivessel and revascularization).mp) or ((multivessel and revascularisation).mp) or ((multi and vessel and revascularization).mp) or ((multi and vessel and revascularisation).mp) or ((multi-vessel and revascularization).mp) or ((multi-vessel and revascularisation).mp)	1,888
4	((non and culprit and coronary and artery).mp) or ((non and culprit and coronary and lesion).mp) or ((non and culprit and lesion).mp) or ((non and culprit).mp) or ((non-culprit and artery).mp) or ((non and culprit and artery).mp) or ((non and culprit and vessel).mp) or ((non-culprit and vessel).mp) or ((non-culprit and lesion).mp) or ((non-infarct-related and artery).mp) or ((non and infarct and related and artery).mp) or ((non and infarct and related and lesion).mp) or ((non-infarct-related and lesion).mp) or ((non-infarct and artery and revascularization).mp) or ((non-infarct and artery and revascularisation).mp) or ((non and infarct and artery and revascularization).mp) or ((non and infarct and artery and revascularisation).mp) or ((non and infarct and revascularization).mp) or ((non and infarct and revascularisation).mp) or ((non and culprit and revascularization).mp)	3,678
5	(exp myocardial infarction/) or ((myocardial and infarction).mp) or ((heart and infarction).mp) or (exp acute coronary syndrome/) or ((acute and coronary and syndrome).mp) or ((STEMI).mp) or ((ST and elevation and myocardial and infarction).mp) or ((ST-elevation and myocardial and infarction).mp) or ((((ST-elevation).mp) or ((ST and elevation).mp) or ((ST-segment-elevation).mp) or ((ST-segment and elevation).mp) or ((ST and segment-elevation).mp) or ((ST and segment and elevation).mp)) AND (((infarct*).mp))) or ((non and ST and elevation and myocardial and infarction).mp) or ((NSTEMI).mp) or ((((non and ST-elevation).mp) or ((non-ST-elevation).mp) or ((non-ST and elevation).mp) or ((non and ST and elevation).mp) or ((non-ST-segment-elevation).mp) or ((non and ST-segment-elevation).mp) or ((non-ST-segment and elevation).mp) or ((non and ST-segment and elevation).mp) or ((non-ST and segment-elevation).mp) or ((non and ST and segment-elevation).mp) or ((non and ST and segment and elevation).mp)) AND (((infarct*).mp)))	146,255
6	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or	2,419,842

	groups.ab.) not (exp animals/ not humans.sh.)	
7	1 AND (2 OR 3 OR 4) AND 5 AND 6	1,282

Table S5. Risk of bias in randomized controlled trials comparing single-stage versus multi-stage complete revascularization

Trial	Sequence Generation	Allocation Concealment	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Role of Funding Source
Sardella et al. (SMILE)[1]	Unclear	Unclear	Low	Unclear	Low	Unclear
Politi et al.[2]	Low	Unclear	Unclear	Low	Low	Unclear
Ochala et al. (PRIMA)[3]	Unclear	Unclear	Unclear	Low	Low	Unclear
Tarasov et al.[4]	Unclear	Unclear	Unclear	Unclear	Low	Unclear

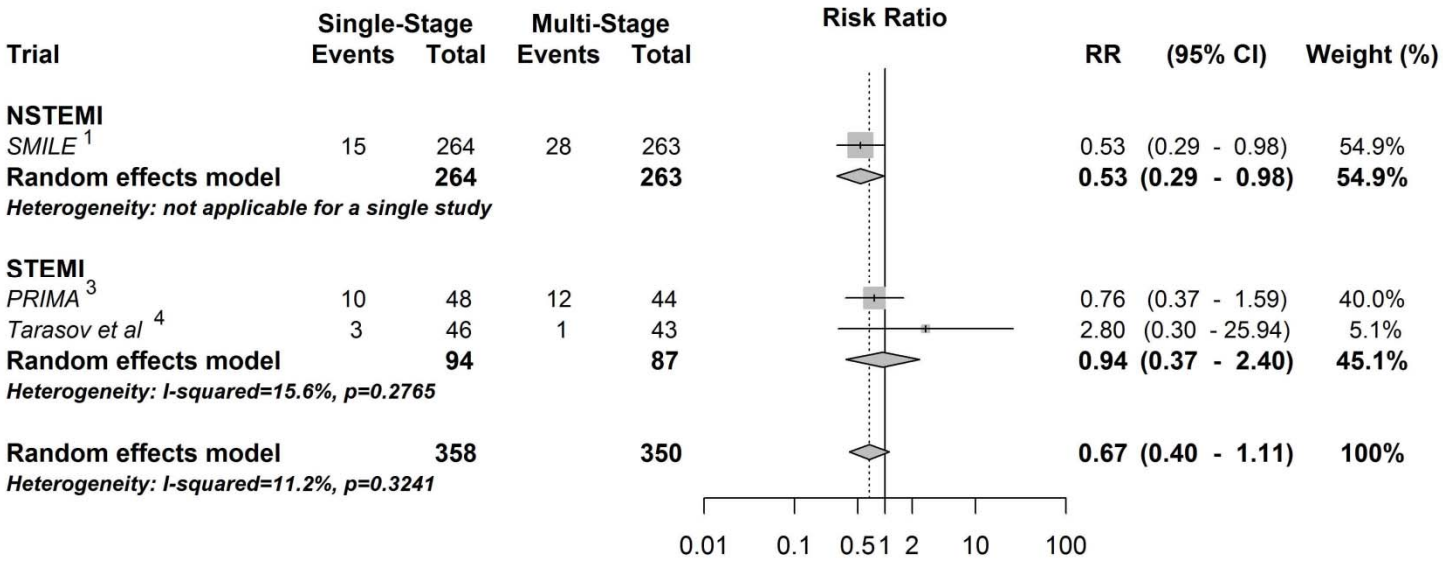
Bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized controlled trials.

Table S6. Incidences of short-term clinical events in randomized controlled trials comparing single-stage and multi-stage complete revascularization*

Trial	MACE		All-Cause Mortality		Cardiovascular Death		Recurrent MI		Repeat Revascularization		Contrast-Induced Nephropathy	
	SS	MS	SS	MS	SS	MS	SS	MS	SS	MS	SS	MS
Sardella et al. (SMILE)[1]	8 (3.03)	6 (2.28)	6 (2.27)	2 (0.76)	4 (1.52)	2 (0.76)	1 (0.38)	1 (0.38)	4 (1.52)	4 (1.52)	0 (0)	0 (0)
Politi et al.[2]	NR	NR	2 (3.08)	0 (0)	NR	NR	NR	NR	NR	NR	1 (1.54)	2 (3.08)
Ochala et al. (PRIMA)[3]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tarasov et al.[4]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

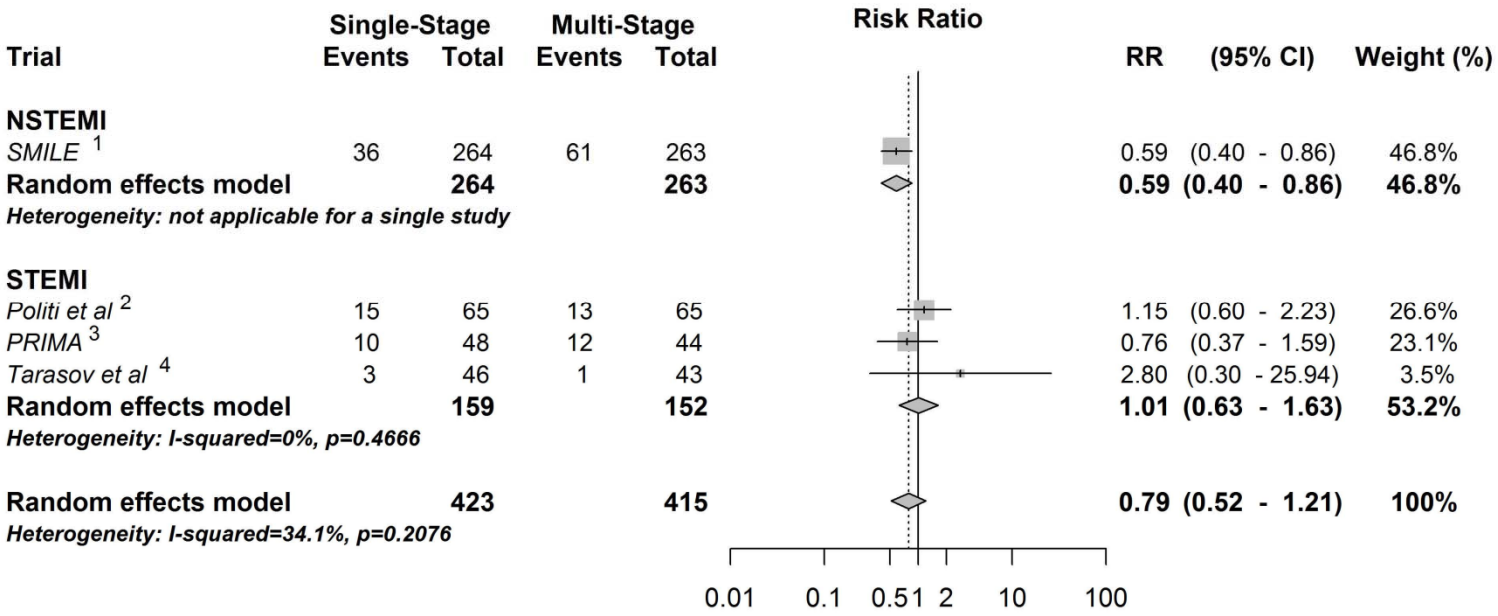
Abbreviations: MACE = major adverse cardiovascular event, MI = myocardial infarction, SS = single-stage complete revascularization, MS = multi-stage complete revascularization, NR = not reported.
*Data are reported as n (%).

Figure S1. Forest plots of subgroup analysis assessing the relative risk of MACE by infarct type at 6 months from randomized controlled trials comparing single-stage to multi-stage complete revascularization.



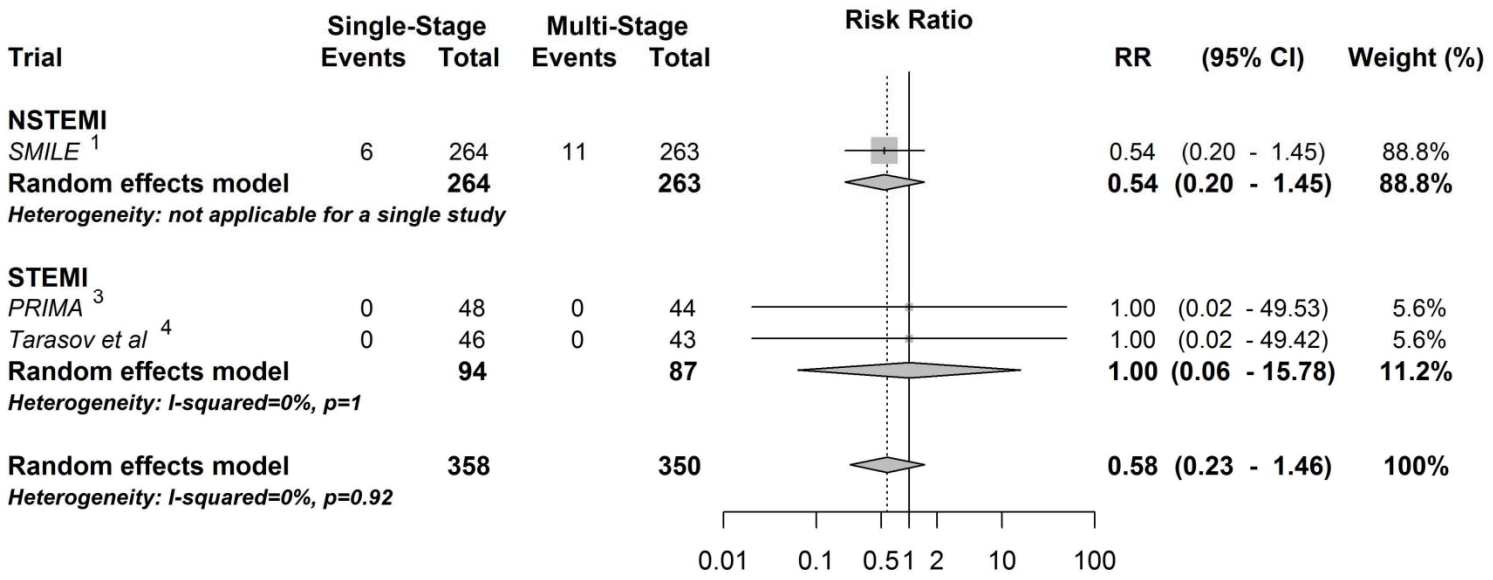
Abbreviations: CI = confidence interval; RR= risk ratio; MACE = Major Adverse Cardiac Event; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S2. Forest plots of subgroup analysis assessing the relative risk of MACE by infarct type at longest follow-up from randomized controlled trials comparing single-stage to multi-staged complete revascularization



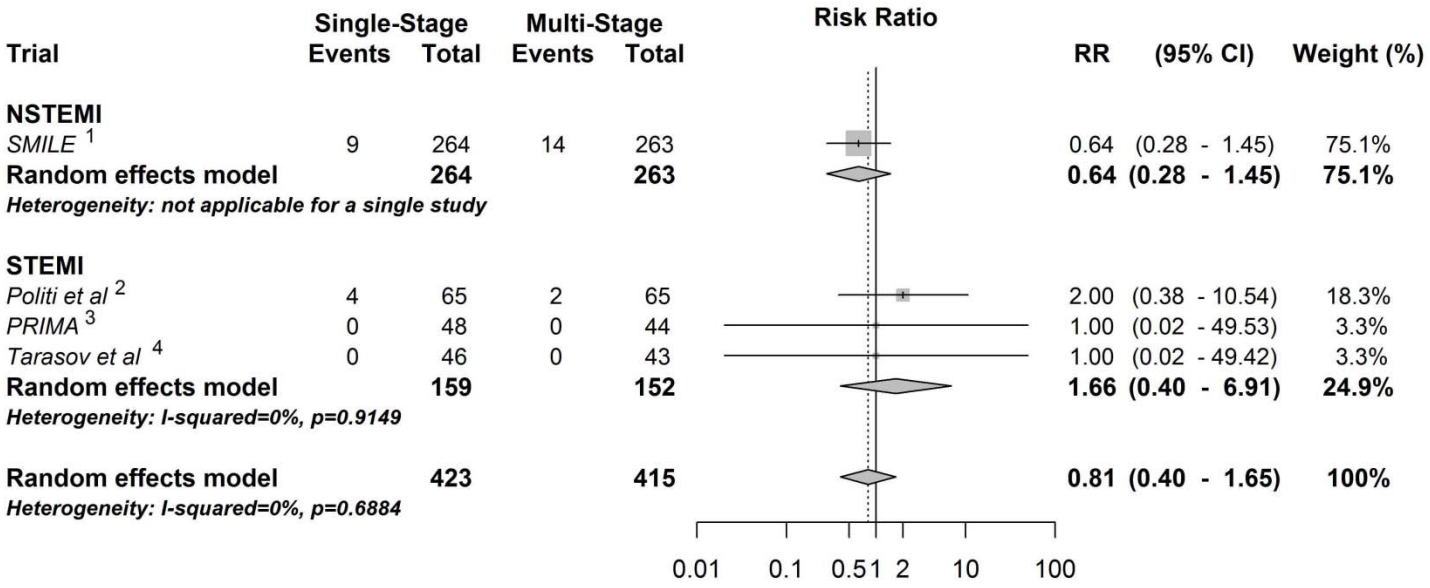
Abbreviations: CI = confidence interval; RR= risk ratio; MACE = Major Adverse Cardiac Event; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S3. Forest plot of subgroup analysis assessing the relative risk of cardiac death by infarct type at 6 months from randomized controlled trials comparing single-stage to multi-stage complete revascularization



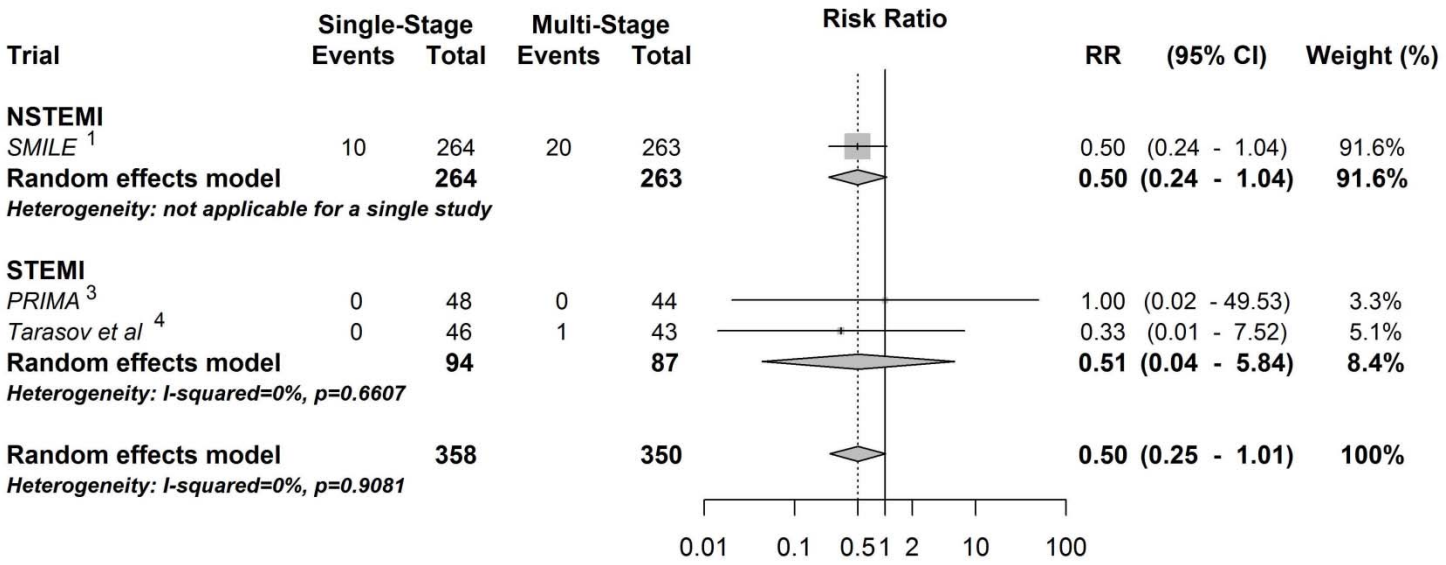
Abbreviations: CI = confidence interval; RR= risk ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S4. Forest plots of subgroup analysis assessing the relative risk of cardiac death by infarct type at longest follow-up from randomized controlled trials comparing single-stage to multi-stage complete revascularization



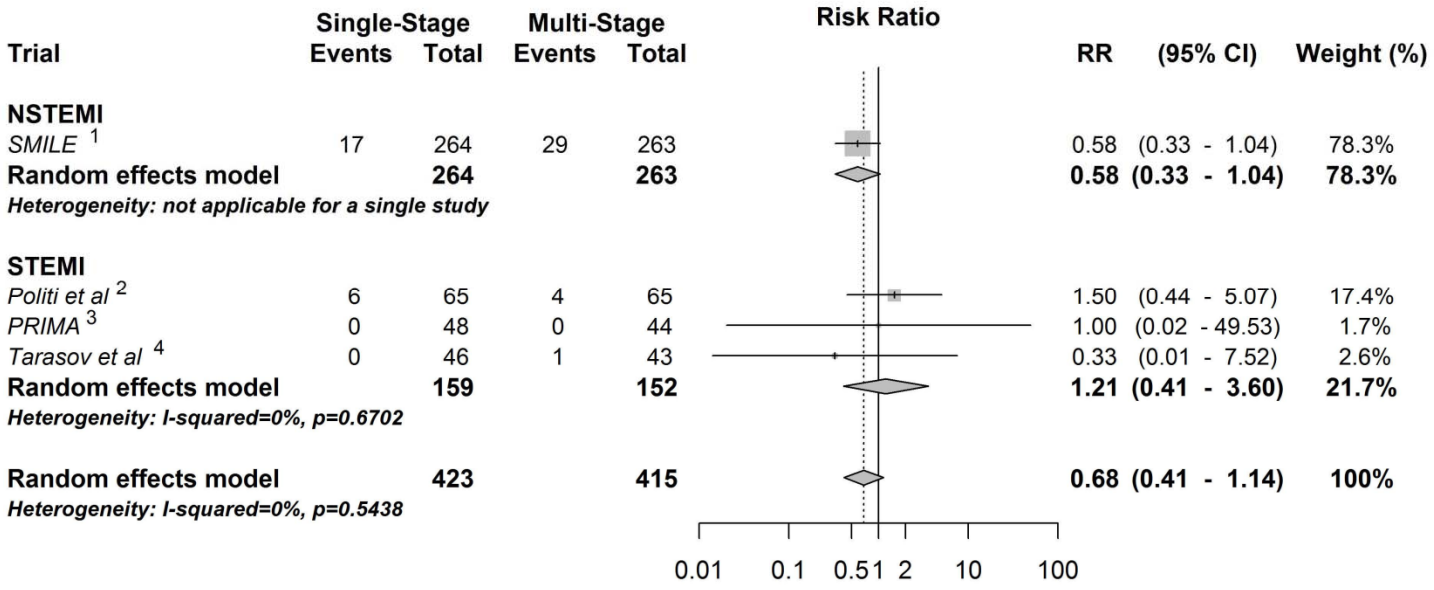
Abbreviations: CI = confidence interval; RR= risk ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S5. Forest plots of subgroup analysis assessing the relative risk of all-cause mortality by infarct type at 6 months from randomized controlled trials comparing single-stage to multi-stage complete revascularization



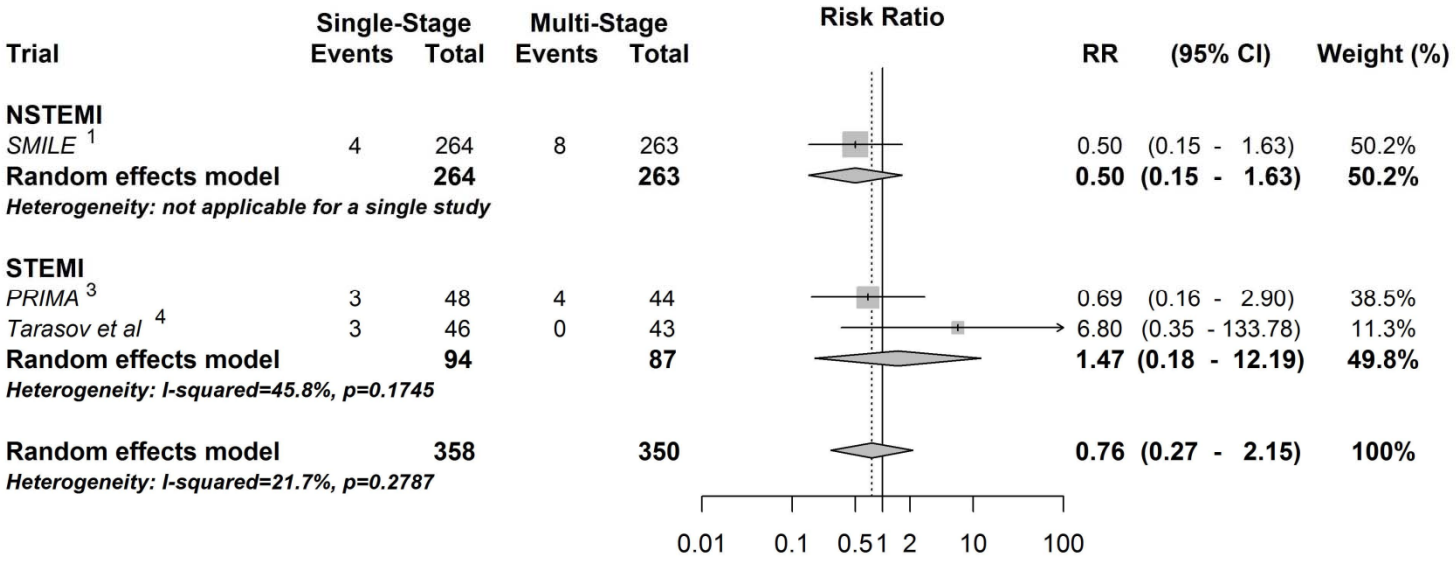
Abbreviations: CI = confidence interval; RR= risk ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S6. Forest plots of subgroup analysis assessing the relative risk of all-cause mortality by infarct type at longest follow-up from randomized controlled trials comparing single-stage to multi-stage complete revascularization



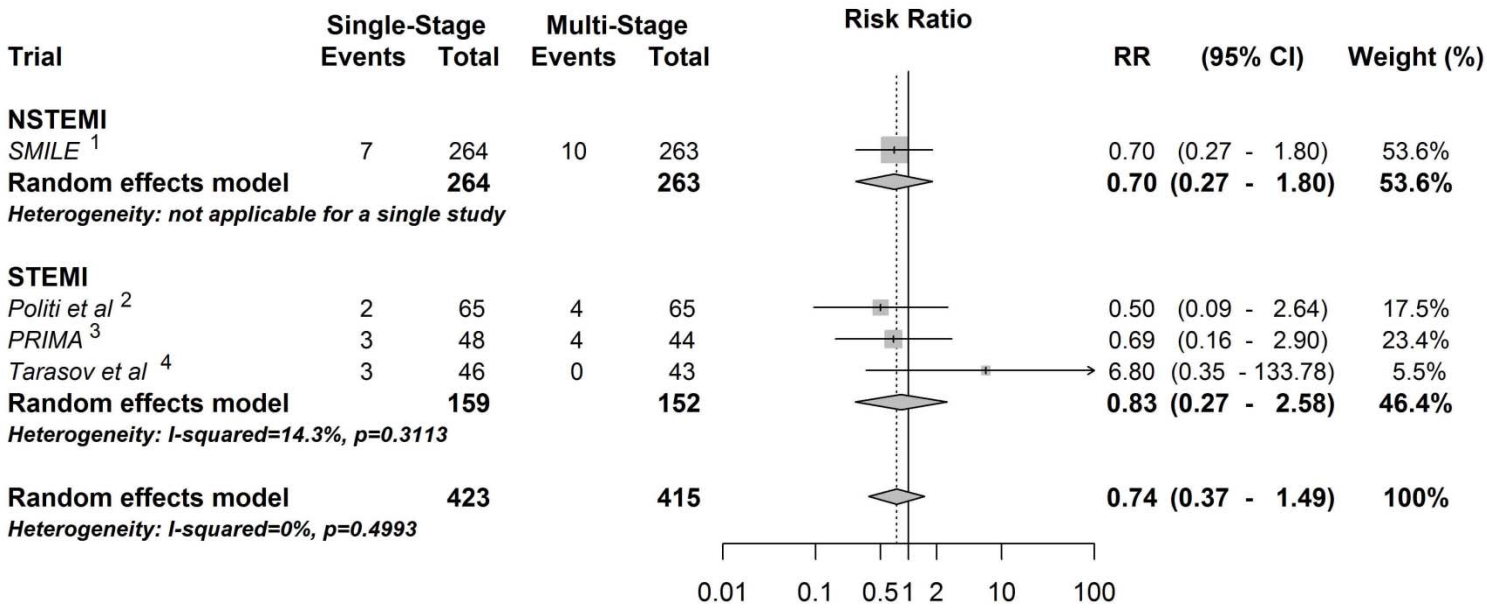
Abbreviations: CI = confidence interval; RR= risk ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S7. Forest plots of subgroup analysis assessing the relative risk of repeat myocardial infarction by infarct type at 6 months from randomized controlled trials comparing single-stage to multi-stage complete revascularization



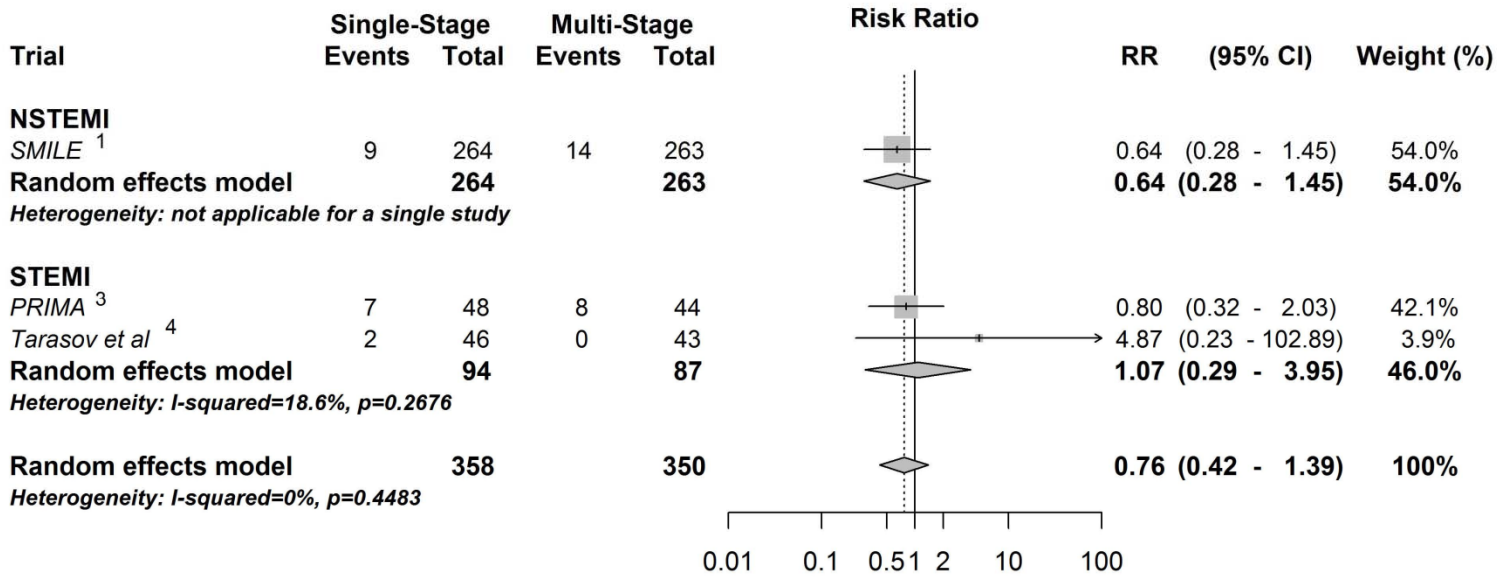
Abbreviations: CI = confidence interval; RR= risk ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S8. Forest plots of subgroup analysis assessing the relative risk of repeat myocardial infarction by infarct type at longest follow-up from randomized controlled trials comparing single-stage to multi-stage complete revascularization



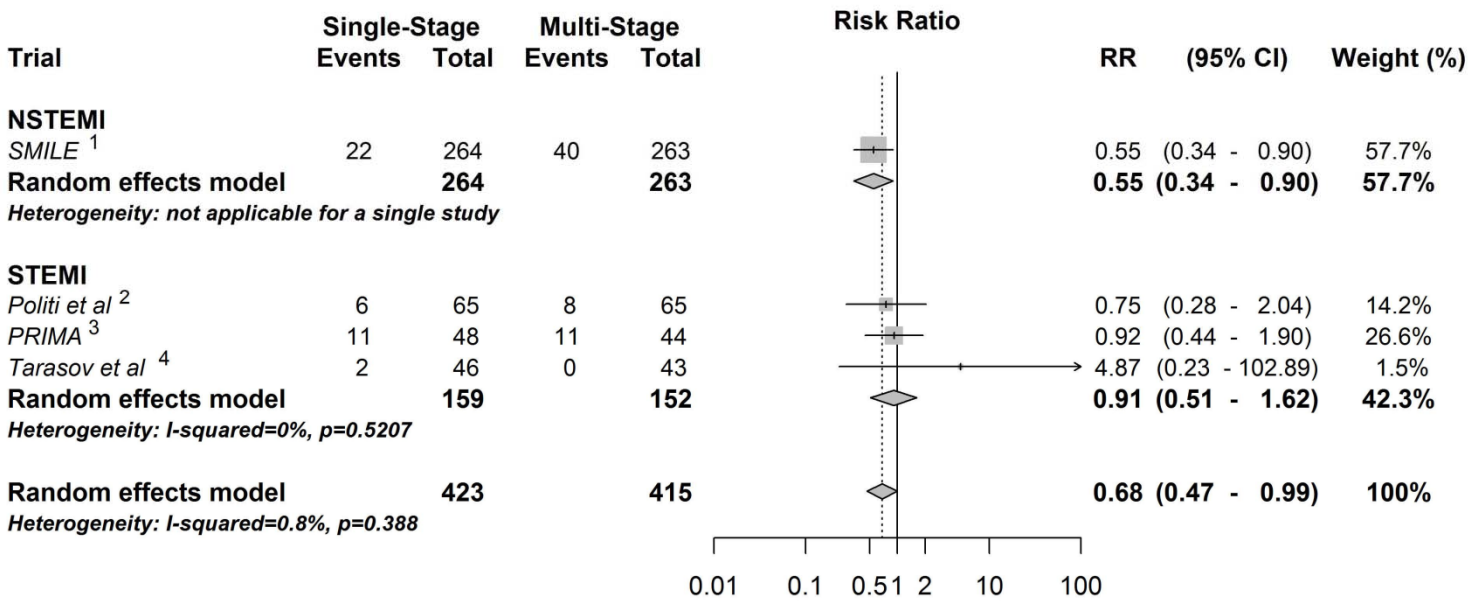
Abbreviations: CI = confidence interval; RR= risk ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S9. Forest plots of subgroup analysis assessing the relative risk of repeat revascularization infarction by infarct type at 6 months from randomized controlled trials comparing single-stage to multi-stage complete revascularization



Abbreviations: CI = confidence interval; RR= risk ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Figure S10. Forest plots of subgroup analysis assessing the relative risk of repeat revascularization by infarct type at longest follow-up from randomized controlled trials comparing single-stage to multi-stage complete revascularization



Abbreviations: CI = confidence interval; RR= relative risk

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3. Ochala A, Smolka GA, Wojakowski W, Dudek D, Dziewierz A, Krolikowski Z, Gasior Z, Tendera M. The function of the left ventricle after complete multivessel one-stage percutaneous coronary intervention in patients with acute myocardial infarction. *J Invasive Cardiol*. 2004;16:699-702
4. Tarasov RS. Six month results of randomized clinical trial: Multivessel stenting in primary percutaneous coronary intervention and staged revascularization for st-elevation myocardial infarction patients with second generation drug eluting stents. *Clinical Medicine Research*. 2014;3:125