

openheart Early versus delayed complete revascularisation in patients presenting with ST-segment elevation myocardial infarction and multivessel disease: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background Several studies have demonstrated that complete revascularisation improves clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary disease. However, the optimal timing of non-culprit lesion revascularisation remains controversial.

Objective The aim of this systematic review and meta-analysis was to assess the effect of timing of complete revascularisation on cardiovascular outcomes in patients with STEMI and multivessel coronary artery disease.

Methods Searches of PubMed, the Cochrane Library, ClinicalTrials.gov and the reference lists of relevant papers were conducted covering the period from 2004 to 2019. A pairwise analysis was performed to compare the difference in clinical outcome between early complete revascularisation (index procedure or index hospitalisation) and delayed complete revascularisation (after discharge) in patients with STEMI.

The primary endpoint was the incidence of major adverse cardiac events (MACE), which was defined as the composite of all-cause mortality, recurrent myocardial infarction, unplanned repeated revascularisation and cardiovascular death.

Results Twelve studies including a total of 7596 patients were identified. The MACE rate was 10.37% in early complete revascularisation compared with 18.17% in culprit only ($p=0.01$). When complete revascularisation was delayed, the MACE rate was 11.81% after complete revascularisation compared with 17.21% in culprit-only percutaneous coronary intervention (PCI) ($p=0.01$). A meta-regression analysis demonstrated no relationship between timing of complete revascularisation and reduction in MACE relative to culprit-only PCI ($p=0.862$).

Conclusion In patients with STEMI treated by primary PCI and multivessel disease, there is a benefit of complete revascularisation over culprit-only PCI whether non-culprit revascularisation is performed early in hospital or delayed as an elective procedure. We have not demonstrated a relationship between timing of complete revascularisation and MACE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The optimal timing of non-culprit lesion revascularisation is still controversial among patients presented with ST-segment elevation myocardial infarction (STEMI) and residual lesions after culprit revascularisation, so our systematic review and meta-analysis was designed to assess the effect of timing of complete revascularisation on major cardiovascular events.

WHAT THIS STUDY ADDS

⇒ The main finding was that early complete revascularisation (index procedure or index hospitalisation) has no significant difference regarding clinical outcomes, but may be favoured in comparison with delayed complete revascularisation (after discharge) and regardless of time, the clinical outcome is better than culprit lesion-only percutaneous coronary intervention (PCI) in patients with STEMI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ We can assume that our paper will have a great impact on the clinical practice and will contribute significantly to the advancement of research in the field.

PROSPERO registration number CRD42021226789.

INTRODUCTION

Primary percutaneous coronary intervention (PPCI) is the gold standard treatment for ST-segment elevation myocardial infarction (STEMI). Multivessel disease is present in ~50% of patients presenting with STEMI and associated with less ST-segment resolution after PPCI and higher 1-year mortality, with a direct proportionality to coronary artery

disease extent in non-culprit vessels.¹ The presence of multivessel disease is associated with worse outcomes relative to single-vessel disease and features of plaque vulnerability are often present. Additionally, atherosclerotic non-culprit plaques may harbour features of vulnerability associated with recurrent atherothrombosis.²

Several randomised trials have demonstrated superior clinical outcomes including cardiovascular death and myocardial infarction with complete revascularisation rather than culprit vessel-only strategy.³ However, the optimal timing of complete revascularisation between index PCI, staged PCI before hospital discharge (early) and staged PCI after discharge (delayed) remains controversial.⁴

The objective of this systematic review is to identify studies involving complete revascularisation in the setting of STEMI and to compare clinical outcomes associated with different intervals from presentation to complete revascularisation.

METHODS

The present systematic review and meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Reviews and Interventions.

Analysis is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement in healthcare interventions.⁵

Search strategy

Searches of PubMed, Google Scholar, Cochrane library, EMBASE and ClinicalTrials.gov, and the reference lists of relevant papers were performed between the years 2004 and 2019.

The following keywords and MeSH terms were used in the searches: “ST-segment elevation myocardial infarction” or “STEMI”, “Complete” or “Non-culprit artery” or “Multivessel”, “Culprit artery” or “Target vessel” or “Infarct related artery” or “IRA” and “Revascularization” or “Percutaneous coronary intervention” or “PCI”.

This meta-analysis was registered at the PROSPERO international prospective register of systematic reviews (Multi-Vessel or Culprit-Only Revascularization in Patients with Multi-Vessel Coronary Artery Disease Undergoing Percutaneous Coronary Intervention; CRD42021226789).

Study selection and eligibility criteria

Two reviewers independently screened the studies including the following:

1. Patients presented with STEMI and multivessel disease.
2. Studies comparing complete revascularisation versus culprit lesion-only PCI.
3. Studies demonstrating specific time/range for complete revascularisation procedure (index procedure or index hospitalisation, or delayed after discharge).
4. Studies reporting the outcomes of major adverse cardiac events (MACE), all-cause mortality, recurrent

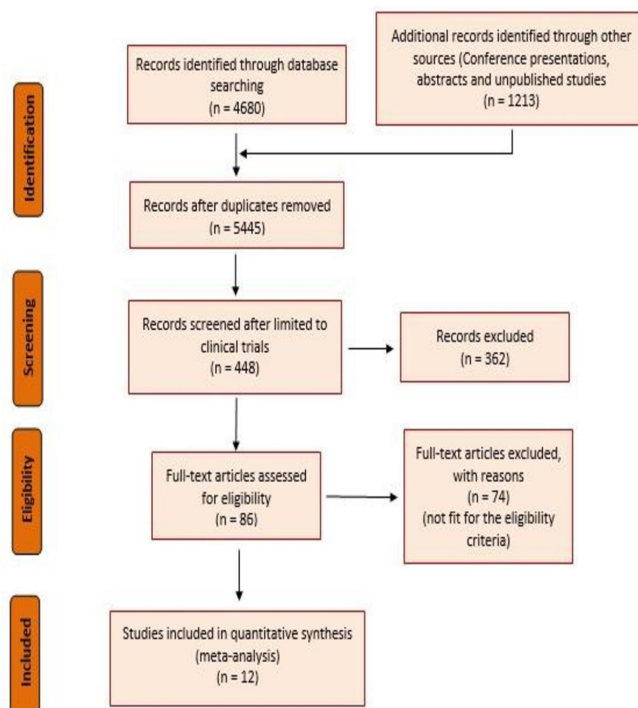


Figure 1 Search strategy and study selection.

myocardial infarction, repeat revascularisation and cardiovascular death.

Studies enrolling patients with a diagnosis other than STEMI or comparing revascularisation strategies other than PCI or trials that solely reported non-clinical outcomes were excluded. Non-randomised controlled trials (RCTs), case reports, editorials, comments, letters, academic conferences and review articles were also excluded from the analysis. A flow chart detailing the literature search and screening process is provided in figure 1.

Data extraction and quality assessment

We developed a data extraction sheet that was subsequently used by two of our authors who independently extracted the following data from the studies included: study name, year, design, number of populations, demographic data (age and gender), risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking), procedure data (number of affected vessels, culprit vessel, number of vessels revascularised, stent type), time of complete revascularisation, follow-up duration and indicators and clinical outcomes.

In the selected studies, the patients were allocated randomly to a group for complete revascularisation of culprit and non-culprit lesions in the same index procedure or in a second procedure just pre-discharge and another group for culprit lesion-only PCI during the index procedure followed by complete revascularisation of the non-culprit lesions after patients' discharge. The decision for patients' allocation was granted either by the study protocol or according to the clinical decision of the treating physician.

We considered 7 days as cut-off point for early complete revascularisation as in the included studies, the index hospitalisation which includes the PPCI only or PPCI and pre-discharge complete revascularisation was up to 7 days' length of stay.

Then we divided the patients into two groups:

Group 1: early complete revascularisation (index procedure or index hospitalisation) <7 days.

Group 2: delayed complete revascularisation (after discharge) ≥7 days.

Only RCTs were included in our meta-analysis. The risk of bias for included RCTs was assessed independently by two reviewers using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials⁶ (online supplemental figure I and online supplemental figure II).

Outcomes and data analysis

Information regarding MACE, all-cause mortality, non-fatal myocardial infarction, unplanned/repeat revascularisation and cardiac death was collected. All endpoints were defined according to the definitions used in each trial.

All outcome comparisons were calculated with RevMan V.5.4 (Cochrane Collaboration, Oxford, UK). The summary relative risks (RRs) and ORs with 95% CIs were estimated using Mantel-Haenszel random-effects method. We calculated the I^2 statistic to evaluate the percentage of heterogeneity among the trials.

A full meta-analysis random-effects approach to the regression had been used, to explore potential relationship in all included studies between the rate of MACE and the time to complete revascularisation.

RESULTS

Our initial search identified 5893 studies, of which 5445 were identified as duplicates and were removed. Four hundred forty-eight studies were screened and 362 were excluded. Eighty-six studies were included for eligibility, of which 74 were excluded. Only 12 studies were included in the final analysis (figure 1).

Eleven studies were included in the final analysis with a total of 7596 patients. Participants' mean age was 61.86 years, 74.29% were male. Summary and population

characteristics of the selected RCTs are shown in online supplemental table II.

One study by Mehta *et al*⁷ reported both early and delayed strategy for complete revascularisation, so it is included in both two groups and comparison analysis.

Seven studies with 5144 patients compared the outcome between early complete revascularisation and culprit lesion-only PCI. The mean time was 1.78 days (figure 2).

Six studies with 2452 patients compared the outcome between delayed complete revascularisation and culprit lesion-only PCI. The mean time was 18.3 days (figure 3).

The meta-analysis demonstrates significant reduction in the outcome in complete revascularisation versus culprit-only PCI when studies undertaking early complete revascularisation were assessed (RR 0.58 (95% CI 0.35 to 0.95)) and also when we assessed those who undertook delayed complete revascularisation (RR 0.68 (95% CI 0.50 to 0.92)). The event rate was 10.37% in early revascularisation compared with 18.17% in culprit only (p=0.01). The event rate was 11.81% in the complete revascularisation arm in studies in which it was delayed compared with 17.21% in culprit only (p=0.01).

Random-effects meta-regression did not reveal any evidence for an association between the log OR for the MACE rate and the time to complete revascularisation (p=0.58). Each trial is represented by a circle and size is proportional to the sample size of each study (figure 4, table 1).

Subgroup analysis

Efficacy of early complete revascularisation versus culprit-only PCI
All-cause mortality

Five studies demonstrated the comparison of all-cause mortality between early complete revascularisation versus culprit lesion-only PCI, and there was no significant effect of early complete revascularisation on all-cause mortality (RR 0.60 (95% CI 0.33 to 1.11) p=0.11) (online supplemental figure III).

Myocardial infarction

Five studies demonstrated the comparison of myocardial infarction between early complete revascularisation versus culprit lesion-only PCI, and there was significant



Figure 2 Forest plot of comparison between early complete revascularisation versus culprit lesion-only PCI.^{11–14} PCI, percutaneous coronary intervention.

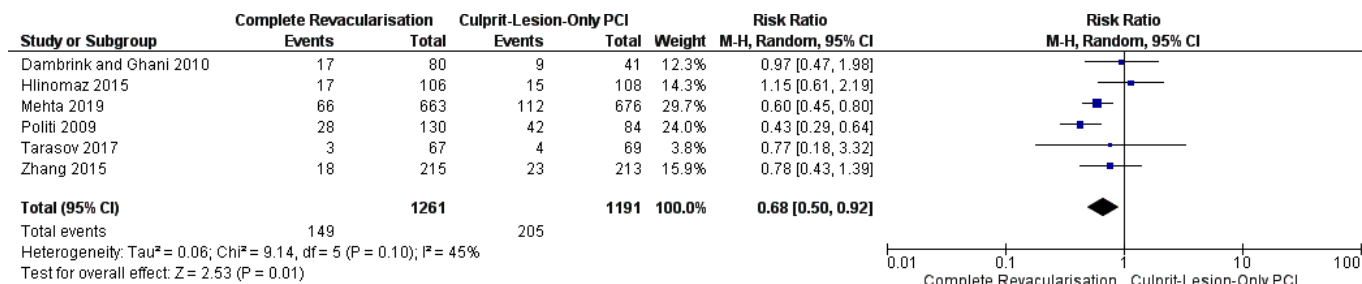


Figure 3 Forest plot of comparison between delayed complete revascularisation and culprit lesion-only PCI.^{15–19} PCI, percutaneous coronary intervention.

difference in the risk of myocardial infarction (RR 0.37 (95% CI 0.26 to 0.54) $p=0.00001$).

Revascularisation

Five studies demonstrated the comparison of revascularisation between early complete revascularisation versus culprit lesion-only PCI, and there was significant reduction in the risk of unplanned revascularisation (RR 0.45 (95% CI 0.31 to 0.66) $p<0.0001$).

Cardiovascular death

Two studies demonstrated the comparison of cardiovascular death between early complete revascularisation versus culprit lesion-only PCI, and there was reduction in the risk of cardiovascular death but not statistically significant (RR 0.47 (95% CI 0.22 to 1.04) $p<0.06$).

The overall effect of combining all endpoints comparing early complete revascularisation versus culprit lesion-only PCI was statistically significant (RR 0.45 (95% CI 0.37 to 0.55) $p<0.00001$).

Efficacy of delayed complete revascularisation versus culprit-only PCI

All-cause mortality

Three studies demonstrated the comparison of all-cause mortality between delayed complete revascularisation versus culprit lesion-only PCI, and there was no significant effect of delayed complete revascularisation on all-cause mortality (RR 0.70 (95% CI 0.44 to 1.13) $p=0.15$) (online supplemental figure IV).

Myocardial infarction

Three studies demonstrated the comparison of myocardial infarction between delayed complete revascularisation

and culprit lesion-only PCI, and there was no difference in the risk of myocardial infarction (RR 0.88 (95% CI 0.52 to 1.47) $p=0.62$).

Revascularisation

Three studies demonstrated the comparison of revascularisation between delayed complete revascularisation and culprit lesion-only PCI, and there was no difference in the risk of unplanned revascularisation (RR 0.96 (95% CI 0.28 to 3.29) $p=0.95$).

Cardiovascular death

Three studies demonstrated the comparison of cardiovascular death between delayed complete revascularisation and culprit lesion-only PCI, and there was no difference in the risk of cardiovascular death (RR 0.59 (95% CI 0.30 to 1.15) $p=0.12$).

The overall effect of combining all endpoints comparing delayed complete revascularisation with culprit lesion-only PCI was statistically non-significant (RR 0.78 (95% CI 0.54 to 1.14) $p<0.19$).

DISCUSSION

The present meta-analysis of randomised and observational studies included 7496 patients comparing the effect of early with delayed complete revascularisation in patients with STEMI. We have demonstrated a benefit in terms of reduction in rate of MACE with complete revascularisation over culprit-only revascularisation, whether the non-culprit revascularisation was performed early or late. We have not demonstrated any relationship between timing of revascularisation in those completely revascularised and differences in clinical outcomes.

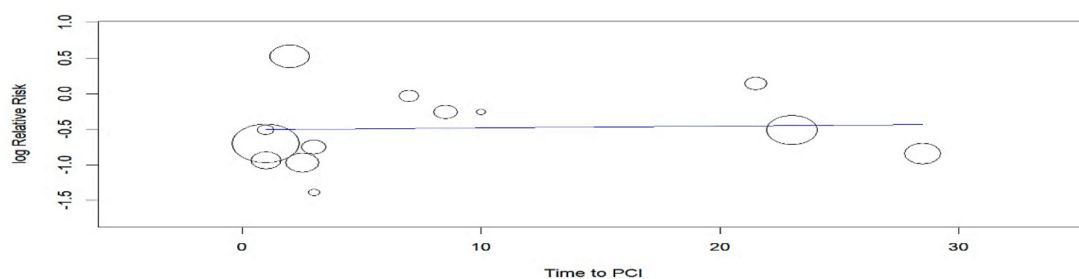


Figure 4 Regression plot of relation between MACE rate and time to complete revascularisation. MACE, major adverse cardiac events; PCI, percutaneous coronary intervention.

Table 1 Regression analysis of relation between MACE rate and time to complete revascularisation.

Covariate	Coefficients	Lower bound	Upper bound	SE	P value
Intercept	-0.509	-0.885	-0.132	0.192	0.008
Time to PCI	0.003	-0.026	0.031	0.014	0.862

Omnibus p value 0.862.
MACE, major adverse cardiac events; PCI, percutaneous coronary intervention.

It is now well established that MACE is reduced by complete revascularisation when compared with culprit-only revascularisation in patients presenting with STEMI.⁸ There has been no randomised comparison to guide timing of non-culprit revascularisation. This could be performed at the time of the index PPCI procedure, staged prior to discharge from hospital (both of which would be considered 'early' in our analysis) or as a staged elective procedure (delayed). Staged, inpatient revascularisation might increase length of stay after presentation with STEMI, such that an early elective procedure might reduce costs. In analysing those studies where complete revascularisation was performed early separately from those in which it was delayed, we have demonstrated a reduction in MACE from both approaches relative to culprit-only PCI. To investigate this further, we performed a meta-regression analysis and demonstrated no relationship between timing of complete revascularisation and altered relative risk of MACE compared with a culprit-only strategy.

In the most recent published trial, COMPLETE,⁷ the largest trial in the field to date, 64% of patients randomised to complete revascularisation had it performed before discharge (median 1 day) and 36% after discharge (median 23 days). A subgroup analysis from this study revealed no difference in outcomes whether total revascularisation was performed early or staged, which was consistent with our findings demonstrated in this meta-analysis.

We have demonstrated a statistically significant benefit for early complete revascularisation with PCI compared with culprit-only PCI in terms of a reduction in myocardial infarction, unplanned revascularisation and cardiovascular death. In the studies in which delayed complete revascularisation was performed, we did not demonstrate a significant reduction in myocardial infarction, cardiovascular death and unplanned revascularisation. Studies, such as DANAMI-3-PRIMULTI⁹ and COMPARE-ACUTE,¹⁰ show that early complete revascularisation of non-culprit vessels was associated with good prognosis when compared with infarct-only PCI.

It is possible that early complete revascularisation might have a greater benefit on the outcomes than a delayed approach. If stunned myocardium in the territory of infarction has not fully recovered, ischaemia or infarction related to a non-culprit stenosis might be more likely to lead to cardiovascular death. Delaying non-culprit revascularisation leaves an interval during which a patient might re-present, prompting unplanned

revascularisation, particularly as physicians are likely to be unblinded to the findings of the index angiogram.

LIMITATIONS

The main limitation to this review is that there are no studies directly comparing early versus delayed revascularisation of non-culprit lesions in the setting of STEMI. Despite the large number of patients included in our analysis, the comparisons of early versus delayed complete revascularisation in this setting are indirect using the same comparator, which is culprit lesion-only PCI, and as such are subject to confounding. Any differences in outcomes between the two groups can only be considered hypothesis generating. An adequately powered randomised trial directly comparing both strategies would be required to address this question more definitively.

CONCLUSION

In patients presenting with STEMI and multivessel disease treated by PPCI, there is a benefit of complete revascularisation over culprit-only PCI, whether the non-culprit revascularisation is performed in hospital or staged as an elective procedure. We have not demonstrated a relationship between timing of complete revascularisation and MACE.

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Ethics approval Not applicable.

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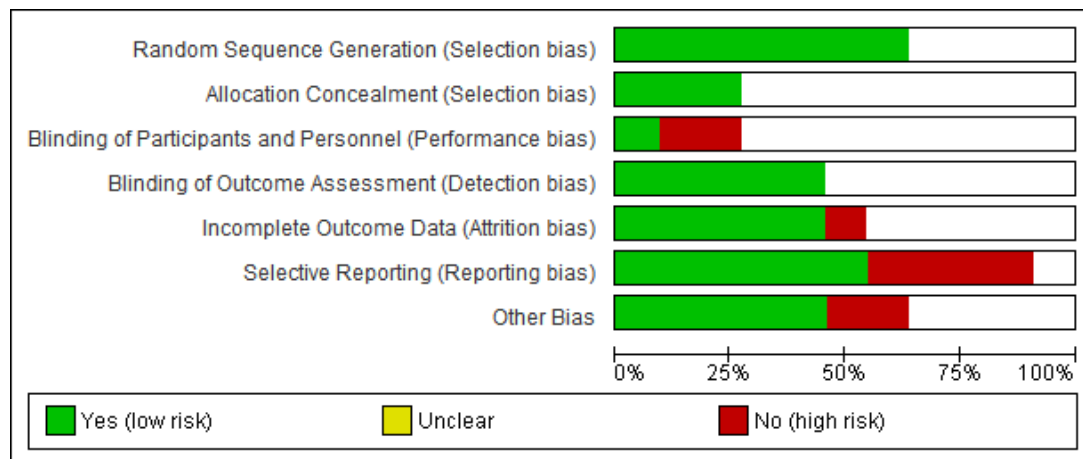
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Supplementary Materials

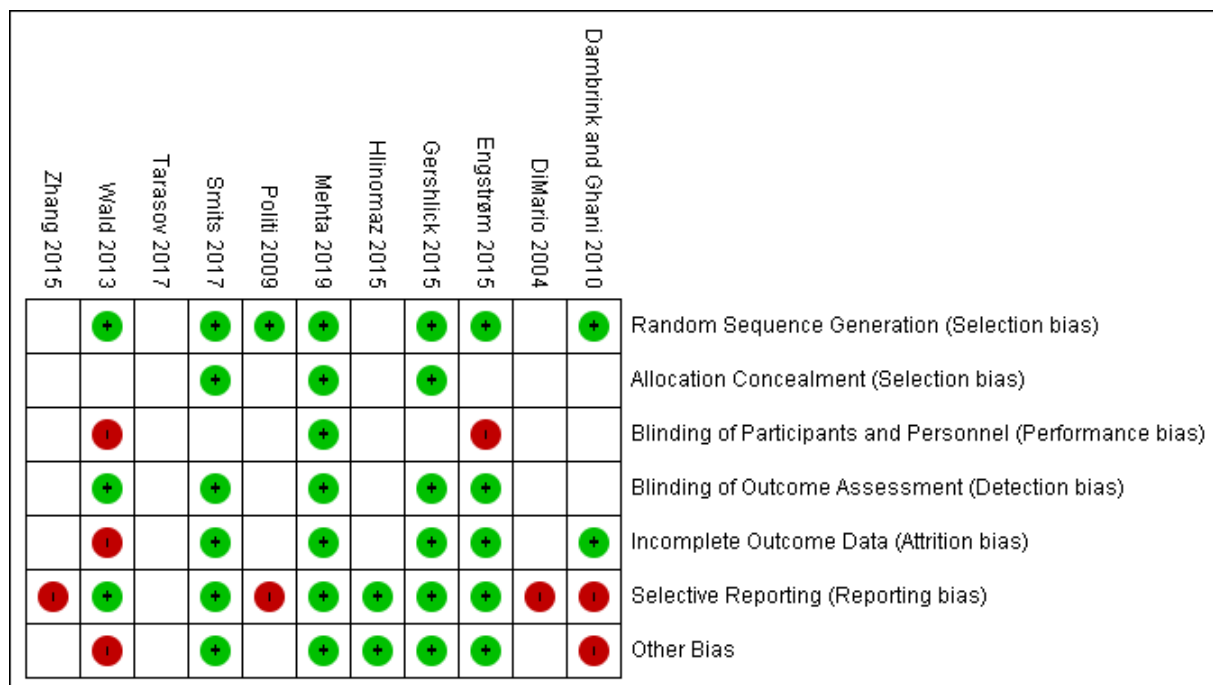
Early versus delayed complete revascularization in patients presenting with ST-segment elevation myocardial infarction and multivessel disease.

A Systematic review and meta-analysis

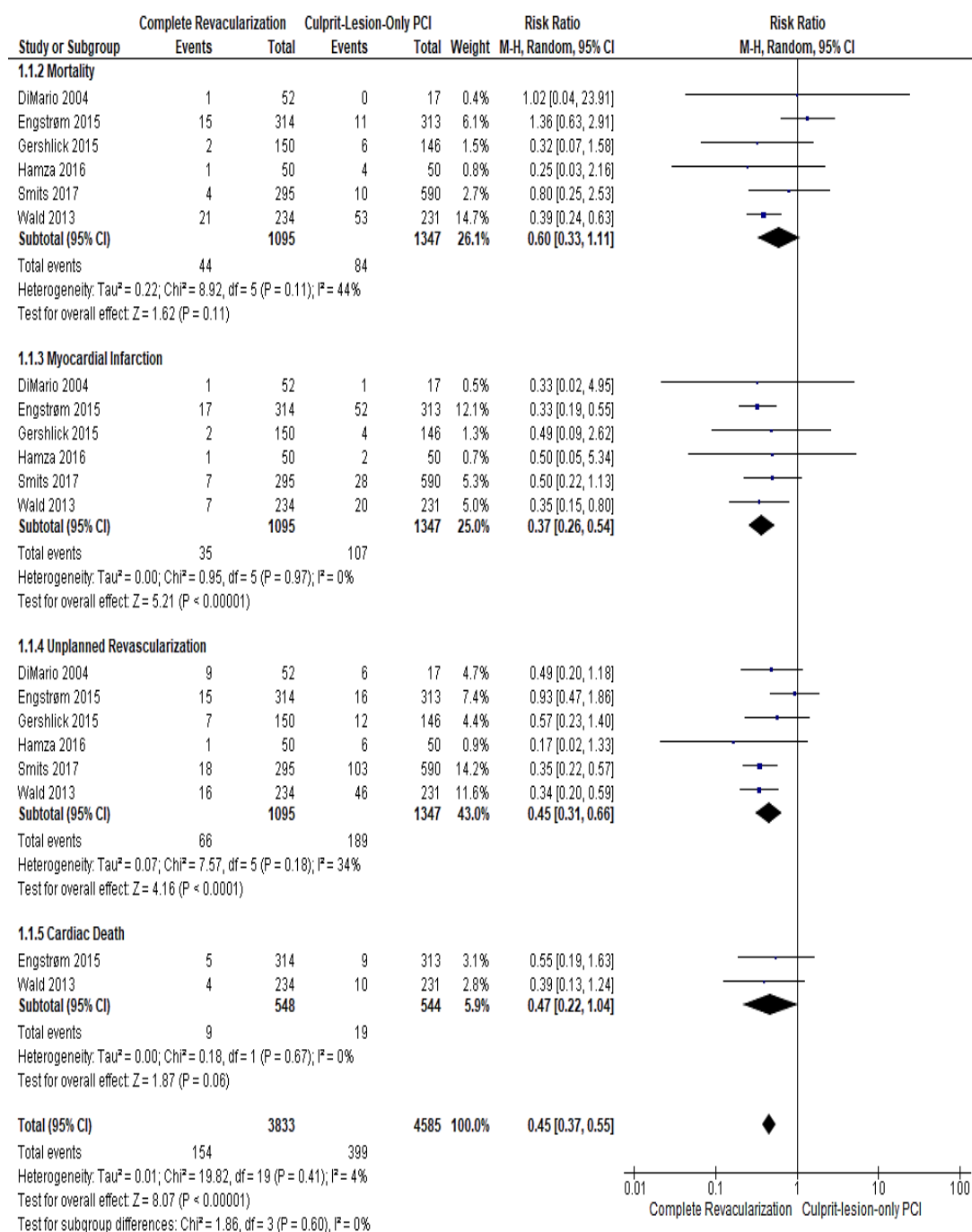
Supplementary Figure I. Risk of bias graph reviews authors' judgements about each risk of bias item presented as percentages across all included studies.



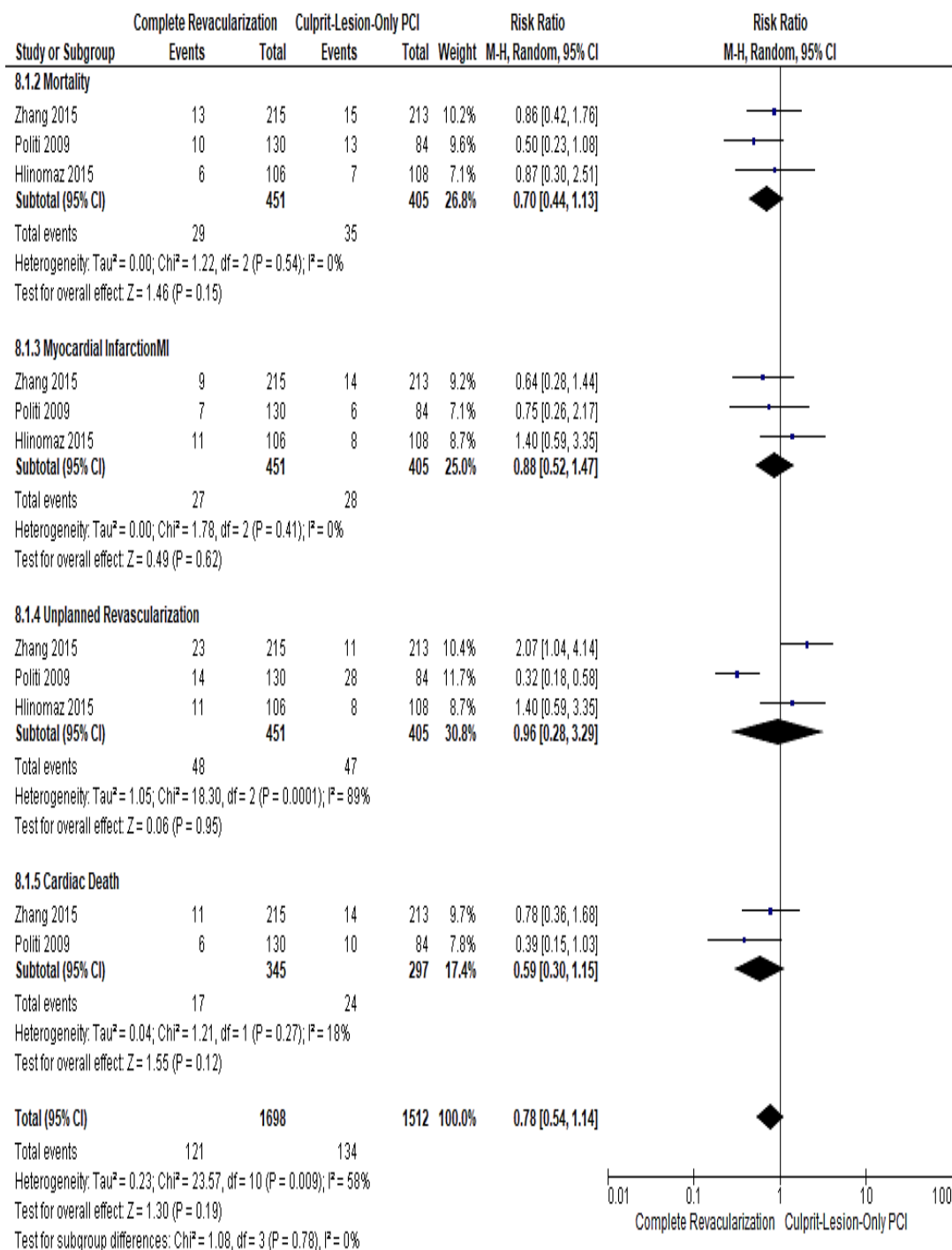
Supplementary Figure II. Risk of bias summary reviews authors' judgements about each risk of bias item for each included study.



Supplementary Figure III: Forest plot of comparison of all-cause mortality, myocardial infarction, unplanned/repeat revascularization, and cardiac death between early complete revascularization versus culprit lesion only PCI.



Supplementary Figure IV: Forest plot of comparison of all-cause mortality, myocardial infarction, unplanned/repeat revascularization, and cardiac death between delayed complete revascularization versus culprit lesion only PCI



Supplementary Table I. Summary and *Population characteristics of the selected randomized controlled trials.*

1st Author	Year	# Population	Sample size	Mean age	# Male	HTN	DM	DLP	Smoking	Prior.MI	Ant.MI	2-Vessel	3-Vessel	DES	BMS	Time/days	F/U indicators	F/U duration/ mo
Mehta ⁷	2019	4041	2016	61.6	1623	982	385	764	819	148	660	459	NR	1704	276	0 - 23	MACE	36
			2025	62.4	1602	1027	402	797	787	154	657	442	NR	1707	272	24 - 45		
Smits ⁹	2017	885	295	62	233	136	43	95	120	22	105	204	91	161	1	index - 4 days	MACE	12
			590	61	450	282	94	176	282	48	206	396	194	NA	NA			
Tarasov ¹⁰	2017	136	67	58.6	48	64	16	NR	NR	NR	NR	35	32	NR	NR	5 - 15	MACE	12
			69	59.1	43	61	14	NR	NR	NR	NR	38	31	NR	NR			
Hamza ¹¹	2016	100	50	56.4	41	13	50	24	36	5	24	36	14	NR	NR	3	MACE	6
			50	52.2	43	18	50	21	39	3	23	33	17	NR	NR			
Zhang ¹²	2015	428	215	62.3	61	64.2	36.7	35.3	NR	NR	36.7	NR	NR	215	0	7 - 10	MACE	24
			213	62	67.1	61	35.2	36.6	NR	NR	40	NR	NR	213	0			
Engström ¹³	2015	627	314	64	251	130	29	NR	NR	17	105	NR	97	298	4	2	MACE	27
			313	63	255	146	42	NR	NR	27	112	NR	100	290	5			
Gershlick ¹⁴	2015	296	150	64.6	128	54	19	41	50	7	54	119	31	141	NR	before discharge (65% index)	MACE	30
			146	65.3	112	51	20	34	37	5	52	110	36	127	NR			
Hlinomaz ¹⁵	2015	214	106	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	3 - 40	MACE	36
			108	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			
Wald ¹⁶	2013	465	234	62	177	94	35	NR	118	19	67	143	91	312	144	index	MACE	23
			231	62	186	93	48	NR	103	16	89	155	76	135	96			
Dambrink and Ghani ¹⁷	2010	121	80	62	64	21	5	12	35	5	17	60	20	18	56	7.5	LVEF (Nuclear & ECHO), ESV, EDV, MACE	6
			41	61	33	17	2	12	19	2	12	33	8	7	27			
Politi ¹⁸	2009	214	130	64.3	102	74	21	NR	NR	NR	59	NR	48	11	NR	56 (50% index)	MACE	30
			84	66.5	64	50	20	NR	NR	NR	35	NR	21	10	NR			
Di Mario ¹⁹	2004	69	52	63.5	46	19	6	21	34	NR	27	36	16	52	0	index	12 mo revascularization, MACE	12
			17	65.3	14	10	7	9	13	NR	10	9	8	17	0			

HTN, hypertension; DM, diabetes mellitus; DLP, dyslipidemia; Ant, Anterior; MI, myocardial infarction; DES, Drug Eluting Stent; BMS, Bare Metal Stent; NR, not reported; MACE, Major Adverse Cardiac Events; LVEF, left ventricular ejection fraction; ESV, EndSystolic Volum; EDV, EndDiastolic Volume.