

CORONARY

# Complete or Culprit-Only Revascularization for Patients With Multivessel Coronary Artery Disease Undergoing Percutaneous Coronary Intervention



## A Pairwise and Network Meta-Analysis of Randomized Trials

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### ABSTRACT

**OBJECTIVES** The authors sought to compare the effectiveness of the different revascularization strategies in ST-segment elevation myocardial infarction (STEMI) patients with multivessel coronary artery disease undergoing primary percutaneous coronary intervention (PCI).

**BACKGROUND** Recent randomized trials have suggested that multivessel complete revascularization at the time of primary percutaneous coronary intervention (PCI) is associated with better outcomes, however; the optimum timing for nonculprit PCI is unknown.

**METHODS** Trials that randomized STEMI patients with multivessel disease to any combination of the 4 different revascularization strategies (i.e., complete revascularization at the index procedure, staged procedure during the hospitalization, staged procedure after discharge or culprit-only revascularization) were included. Random effect risk ratios (RRs) were conducted. Network meta-analysis was constructed using mixed treatment comparison models, and the 4 revascularization strategies were compared.

**RESULTS** A total of 10 trials with 2,285 patients were included. In the pairwise meta-analysis, complete revascularization (i.e., at the index procedure or as a staged procedure) was associated with a lower risk of major adverse cardiac events (MACE) (RR: 0.57; 95% confidence interval [CI]: 0.42 to 0.77), due to lower risk of urgent revascularization (RR: 0.44; 95% CI: 0.30 to 0.66). The risk of all-cause mortality (RR: 0.76; 95% CI: 0.52 to 1.12), and spontaneous reinfarction (RR: 0.54; 95% CI: 0.23 to 1.27) was similar. The reduction in the risk of MACE was observed irrespective of the timing of nonculprit artery revascularization in the mixed treatment model.

**CONCLUSIONS** Current evidence from randomized trials suggests that the risk of all-cause mortality and spontaneous reinfarction is not different among the various revascularization strategies for multivessel disease. Complete revascularization at the index procedure or as a staged procedure (either during the hospitalization or after discharge) was associated with a reduction of MACE due to reduction in urgent revascularization with no difference between these 3 strategies. Future trials are needed to determine the impact of complete revascularization on the risk of all-cause mortality and spontaneous reinfarction. (J Am Coll Cardiol Intv 2017;10:315-24) © 2017 by the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

**ABBREVIATIONS  
AND ACRONYMS****CI** = confidence interval**MACE** = major adverse cardiac event(s)**PCI** = percutaneous coronary intervention**RR** = risk ratio**STEMI** = ST-segment elevation myocardial infarction

**P** rimary percutaneous coronary intervention (PCI) remains the cornerstone for treatment of patients with ST-segment elevation myocardial infarction (STEMI) (1,2). Approximately one-half of the patients exhibit 1 or more concomitant obstructive coronary lesion (i.e., nonculprit or multivessel disease) at the time of primary PCI. These patients tend to have worse short-term and long-term mortality and morbidity compared with subjects with less extensive coronary artery disease (3,4). Earlier observational studies had demonstrated that revascularization of the nonculprit-related artery during primary PCI was

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associated with worse outcomes (5,6). Recent randomized trials and meta-analyses have challenged these findings (7-13); however, the utility and timing of additional revascularization in patients with multivessel disease remain unclear. Recently, the American College of Cardiology Foundation/American Heart Association guidelines for nonculprit vessel revascularization in STEMI patients with multivessel disease were modified to a Class IIb indication (can be considered) from an earlier Class III indication (harm), reflecting the uncertainty in this field (14). Thus, we first sought to conduct a pairwise meta-analysis to assess the efficacy of nonculprit PCI in STEMI patients with multivessel disease. Further, we sought to conduct a network meta-analysis to assess the relative merits of additional revascularization during primary PCI or as a staged procedure either during the index hospitalization or after discharge.

**METHODS**

**DATA SOURCES.** An electronic search of MEDLINE, Web of Science, the Cochrane database (CENTRAL), and Google Scholar along with major conference proceedings was conducted from inception through October 2016 with no language restriction using the Medical Subject Heading and the key word search terms “percutaneous coronary intervention,” “myocardial infarction,” and “multivessel.” The bibliography of the retrieved articles and prior meta-analyses were reviewed. 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; CRD42016042121).

**SELECTION CRITERIA.** Four different revascularization strategies are available for the treatment of multivessel disease at the time of primary PCI: 1) complete revascularization at the index procedure in which the culprit artery (i.e., infarct-related artery) as well as  $\geq 1$  nonculprit artery were treated during the index procedure; 2) complete revascularization as a staged procedure in which the culprit artery was treated at the index procedure whereas the nonculprit artery was treated before discharge (i.e., during the index hospitalization); 3) complete revascularization as a staged procedure in which the culprit artery was treated at the index procedure whereas the nonculprit artery was treated within a few weeks after discharge (i.e., the staged procedure

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was planned and not symptom driven); and 4) culprit-only revascularization in which the culprit artery only was treated. For the purpose of this meta-analysis, we included only randomized clinical trials that compared any combination of these 4 strategies (i.e., the trials could compare 2 or 3 strategies).

In the pairwise meta-analysis, complete revascularization (i.e., either complete revascularization at the index procedure or as a staged procedure either during the hospitalization or after discharge) was compared with culprit-only revascularization strategy. In the network meta-analysis, subjects were divided into 4 groups depending on the revascularization strategy (i.e., complete revascularization at the index procedure, complete revascularization as a staged procedure during the hospitalization, complete revascularization as a staged procedure after discharge, or culprit-only revascularization). The quality of the included trials was evaluated based on the adequate description of treatment allocation, blinded outcome assessment, and description of losses to follow-up (15).

**DATA EXTRACTION.** Two independent authors (I.Y.E. and A.N.M.) extracted the data on the study design, sample size, interventional strategies, and clinical outcomes. Any discrepancies were resolved by consensus. The number of events that occurred in each arm of the trial was tabulated.

**OUTCOMES.** The main outcome for this analysis was major adverse cardiac events (MACE) defined as per the individual trials (Online Table 1-A). Other outcomes evaluated in this analysis included: all-cause mortality, reinfarction defined as spontaneous reinfarction (i.e., trials that included peri-procedural myocardial infarction as part of the definition or trials that did not define reinfarction were excluded from the analysis for reinfarction) (Online Table 1-B), and revascularization (defined as ischemia-driven or urgent). We preferentially utilized data from the longest available follow-up whenever applicable. In this analysis, we have not focused on safety outcomes (i.e., major bleeding, contrast-induced nephropathy, contrast volume, and procedure time) because we reported these outcomes in a previous publication (11), and the data were not sufficient to perform a network meta-analysis comparing the 4 different revascularization strategies for these outcomes.

**STATISTICAL ANALYSIS.** This meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (16). Outcomes were analyzed by an intention-to-treat analysis. All analyses for the pairwise meta-analysis were performed using STATA

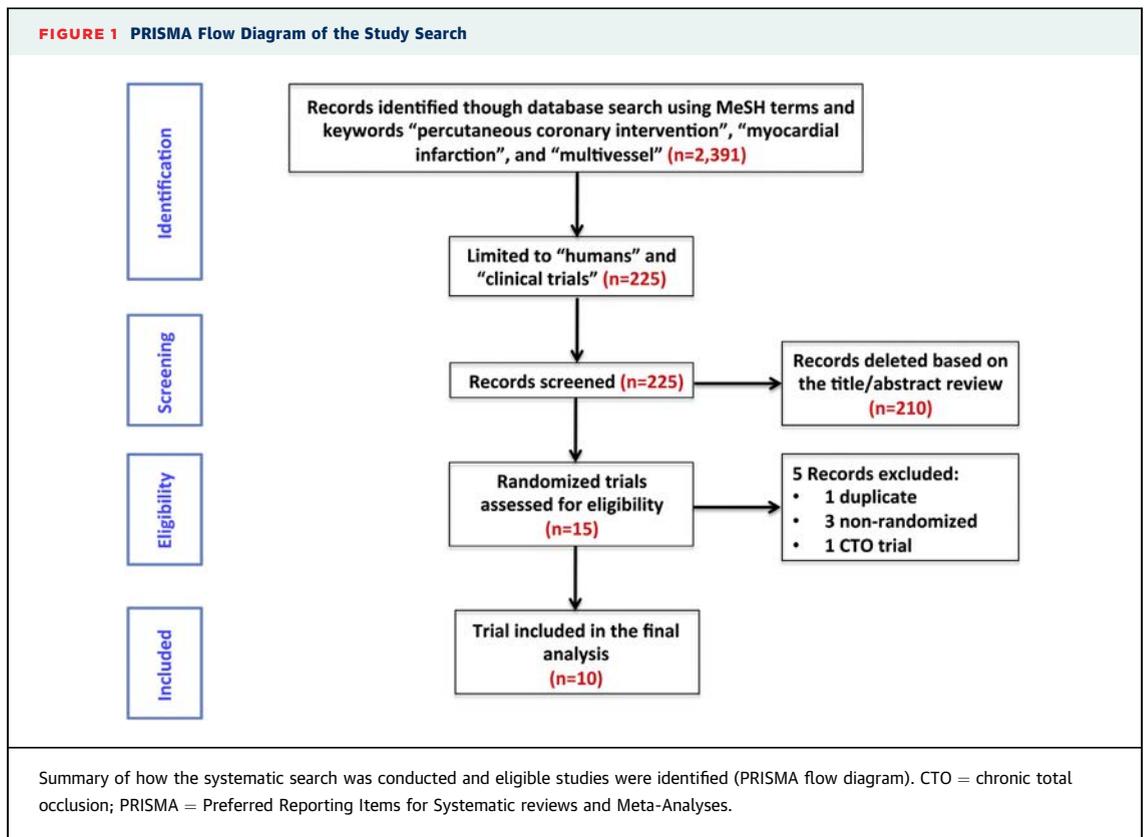
software version 14 (STATA Corporation, College Station, Texas). Summary estimate risk ratios (RRs) were constructed with a DerSimonian and Laird model (17). Statistical heterogeneity was examined using the  $I^2$  statistic (18). Egger's method was used to estimate publication bias (19). All p values were 2-tailed, with statistical significance set at 0.05, and confidence intervals (CIs) were calculated at the 95% level. For the main outcome (i.e., MACE), the following sensitivity analyses were performed: 1) excluding trials that did not include urgent revascularization as part of the MACE definition; 2) excluding trials yet to be published; 3) excluding older trials (i.e., before 2010); and 4) limiting an analysis to trials that included at least 100 patients in each arm.

The network meta-analysis was performed using a random effects model in order to account for the heterogeneity between the trials (20). All analyses for the network meta-analysis were conducted using the "mvmeta" command and self-programmed software routines (STATA software). Inconsistency was examined by comparing the deviance residuals and deviance information criterion statistics in fitted consistency and inconsistency models.

## RESULTS

**INCLUDED STUDIES.** The electronic search yielded 225 articles that were screened by reviewing the title and/or abstract. One study reported outcomes at both a short-term and long-term follow-up periods (21,22), so we included only the longer follow-up (22). Two studies comparing complete revascularization at the index procedure and complete revascularization as a staged procedure were not included because they were not truly randomized (23,24). A prospective nonrandomized study that compared complete revascularization at the index procedure and culprit-only revascularization was not included as well (25). One randomized trial tested the efficacy of staged PCI of chronic total occlusions, thus it was excluded (26). Figure 1 reported the search strategy and how the eligible studies were identified.

A total of 10 trials with 2,285 patients were included in the final analysis (7-9,22,27-32). The follow-up time ranged from 6 to 38 months (median 25 months). Patients with cardiogenic shock upon presentation were explicitly excluded. One of the trials is yet to be published (28). Two trials compared a complete revascularization at the index procedure versus complete revascularization as a staged procedure after discharge (29,32); therefore, these studies were not included in the pairwise meta-analysis. Three trials compared 3 different revascularization strategies



(8,27,30). Fractional flow reserve was used to stratify patients with multivessel disease in 2 trials (9,22); with 1 trial using a cutoff  $\leq 0.80$  for revascularization (9), whereas the other used  $\leq 0.75$  (22). **Table 1** reports the characteristics of the included studies. Overall, the included studies were classified as low-to-intermediate risk for bias. **Online Table 2** summarizes the measures of study quality.

In CvLPRIT (Complete versus Lesion-only Primary percutaneous coronary Intervention Trial), 64% of the patients randomized to complete revascularization underwent complete revascularization at the index procedure (8). Only the outcome of MACE was reported for both complete revascularization at the index procedure and complete revascularization at the staged procedure during the hospitalization; therefore, we included the CvLPRIT trial in the network meta-analysis only for the outcome of MACE, whereas we included this trial for all outcomes in the pairwise meta-analysis. For the CvLPRIT trial, we included only the spontaneous reinfarction events in the analysis of reinfarction (data about spontaneous reinfarction was reported separately in this trial) (8), whereas Ghani et al. (22) did not report separate events for

spontaneous reinfarction, thus this study was excluded from the spontaneous reinfarction analysis (**Online Table 1-B**). In **Online Table 3**, we report the trials that were included in the analysis of the individual outcomes of interest.

**PAIRWISE META-ANALYSIS.** Compared with a culprit-only revascularization strategy, a complete revascularization strategy (i.e., either at the time of the index procedure or as a staged procedure during the hospitalization or after discharge) was associated with a lower risk of MACE (14.6% vs. 24.4%; RR: 0.57; 95% CI: 0.42 to 0.77;  $p < 0.0001$ ;  $I^2 = 57\%$ ) (**Figure 2**). This was entirely due to a lower risk of urgent revascularization in the complete revascularization group (9.0% vs. 18.6%; RR: 0.44; 95% CI: 0.30 to 0.66;  $p < 0.0001$ ;  $I^2 = 56\%$ ) (**Figure 2**). The risk of all-cause mortality (4.6% vs. 5.8%; RR: 0.76; 95% CI: 0.52 to 1.12;  $p = 0.17$ ;  $I^2 = 2\%$ ), and spontaneous reinfarction (3.1% vs. 5.5%; RR: 0.54; 95% CI: 0.23 to 1.27;  $p = 0.16$ ;  $I^2 = 47\%$ ) was similar in both groups (**Figure 2**). There was no evidence of publication bias with Egger's test for any of the outcomes assessed. In **Table 2**, we summarize the outcomes assessed in the pairwise meta-analysis.

**TABLE 1** Characteristics, Follow-Up Duration, and the Interventional Strategies of the Included Studies

First Author/Trial (Ref. #)	Year	Complete Revascularization as Index Procedure, n	Complete Revascularization as Staged Procedure, n	Culprit-Only Revascularization, n	Follow-Up, Months	Type of Complete Revascularization	Timing of Staged-Procedure, Days
Hamza et al. (27)	2016	29	21	50	6	Index and staged	Hospitalization
PRAGUE 13 (28)	2015	NA	106	108	38	Staged only	3-40*
DANAMI-3-PRIMULTI (9)	2015	Not applicable	314	313	27	Staged only	2
CvLPRIT (8)	2015	97	42	146	12	Index and staged	Hospitalization
Tarasov et al. (29)	2014	46	43	Not applicable	6	Index and staged	8.5†
PRAMI (7)	2013	234	Not applicable	231	23	Index only	Not applicable
Ghani et al. (22)	2012	Not applicable	79	40	36	Staged only	7.5‡
Politi et al. (30)	2010	65	Excluded	84	30	Index and staged	Not applicable
HELP AMI (31)	2004	52	Not applicable	17	6	Index only	Not applicable
PRIMA (32)	2004	48	44	NA	12	Index and staged	27.3†

\*Range. †Mean. ‡Median.

CvLPRIT = complete versus lesion-only Primary PCI pilot study; DANAMI-3-PRIMULTI = third danish study of primary PCI in patients with ST-elevation myocardial infarction and multivessel disease; treatment of culprit lesion only or complete revascularization; HELP-AMI = HEpacoat for cuLPrIt or multivessel stenting for acute myocardial infarction; PRAMI = preventive angioplasty in acute myocardial Infarction.

For the outcome of MACE, the results of the sensitivity analyses were consistent with the main analysis: 1) excluding trials that did not include urgent revascularization as part of the MACE definition (RR: 0.56; 95% CI: 0.41 to 0.75;  $p < 0.0001$ ); 2) excluding trials yet to be published (RR: 0.52; 95% CI: 0.40 to 0.69;  $p < 0.0001$ ); 3) excluding older trials (RR: 0.57; 95% CI: 0.41 to 0.79;  $p = 0.001$ ); and 4) limited to trials that included at least 100 patients in each arm (RR: 0.57; 95% CI: 0.39 to 0.85;  $p = 0.006$ ). There was no difference in the treatment effect when the larger trials (i.e., at least 100 patients in each arm) were compared with the smaller trials (i.e., <100 patients in each arm) (RR: 0.55; 95% CI: 0.42 to 0.77;  $p = 0.04$ );  $P_{interaction} = 0.93$ .

**NETWORK META-ANALYSIS.** The mixed treatment model showed that complete revascularization at the index procedure (RR: 0.37; 95% CI: 0.24 to 0.59), as a staged procedure during the hospitalization (RR: 0.49; 95% CI: 0.27 to 0.91), and as a staged procedure after discharge (RR: 0.58; 95% CI: 0.35 to 0.97) were associated with a lower risk of MACE compared with a culprit-only revascularization strategy. There was no difference between complete revascularization at the index procedure, complete revascularization as a staged procedure during the hospitalization or after discharge (Figure 3). Similarly, mixed treatment models showed that complete revascularization at the index procedure (RR: 0.32; 95% CI: 0.19 to 0.54), as a staged procedure during the hospitalization (RR: 0.31; 95% CI: 0.15 to 0.65), and as a staged procedure

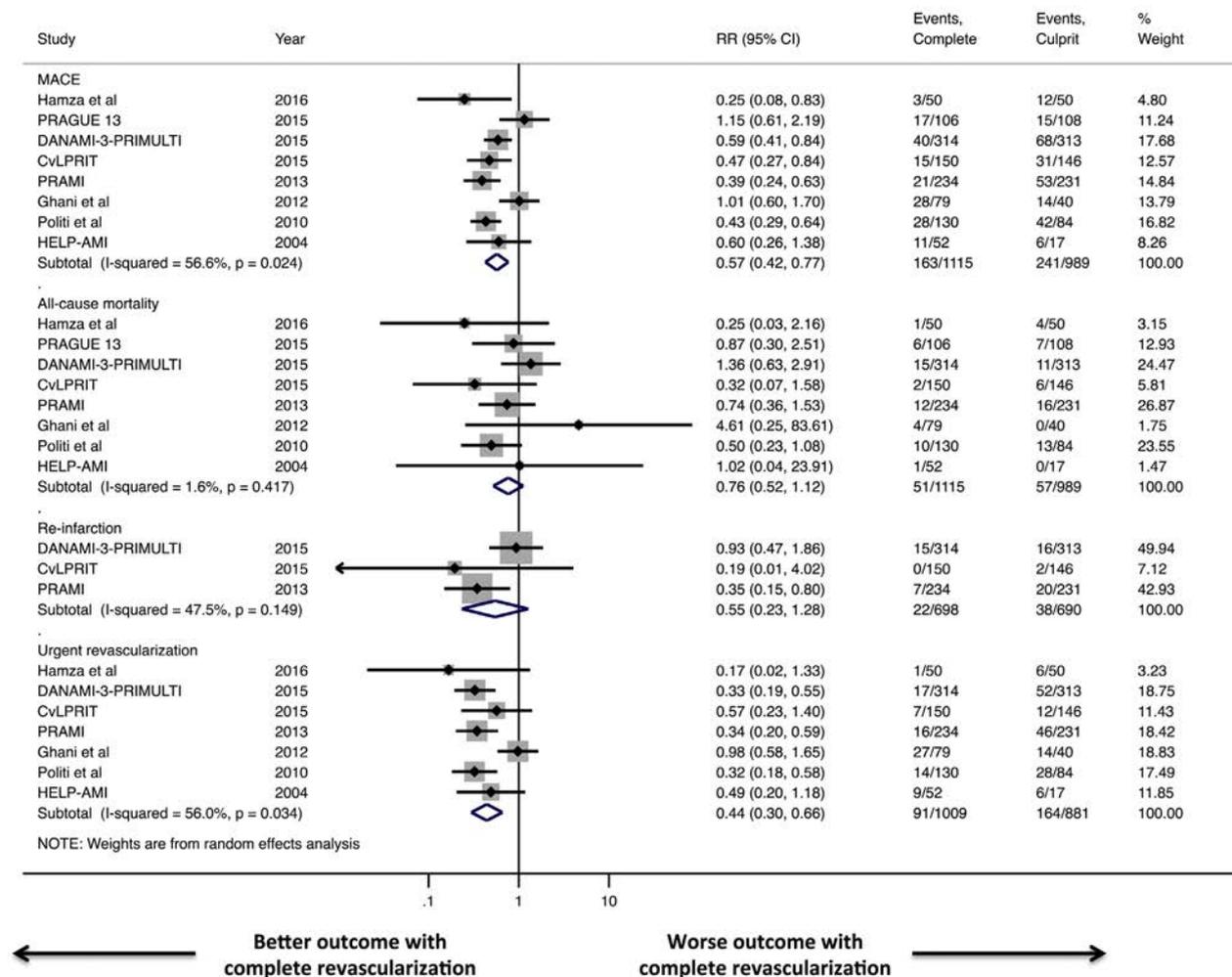
after discharge (RR: 0.46; 95% CI: 0.25 to 0.85) were associated with a lower risk of urgent revascularization with no difference between complete revascularization at the index procedure or as a staged procedure either during the hospitalization or after discharge. There was no difference in the risk of all-cause mortality among the 4 revascularization strategies (Figure 3). A mixed treatment model could not be performed for the outcome of spontaneous reinfarction due to the limited number of studies included in this analysis (i.e., 3 trials only) (Online Table 3).

## DISCUSSION

In this comprehensive meta-analysis of 10 randomized trials with 2,285 patients, we aimed to compare the outcomes with the 4 different revascularization strategies for patients with multivessel coronary artery disease undergoing primary PCI. We demonstrated that there was no difference among the 4 strategies in the risk of all-cause mortality and spontaneous reinfarction at a median of 25 months. A complete revascularization strategy at the index procedure or as a staged procedure whether during the hospitalization or after discharge was associated with a reduction in the risk of MACE. This effect was only due to a reduction in the risk of urgent revascularization.

Earlier observational studies had suggested that complete revascularization for multivessel disease at the time of primary PCI might be harmful (5,6).

**FIGURE 2** Pairwise Meta-Analysis

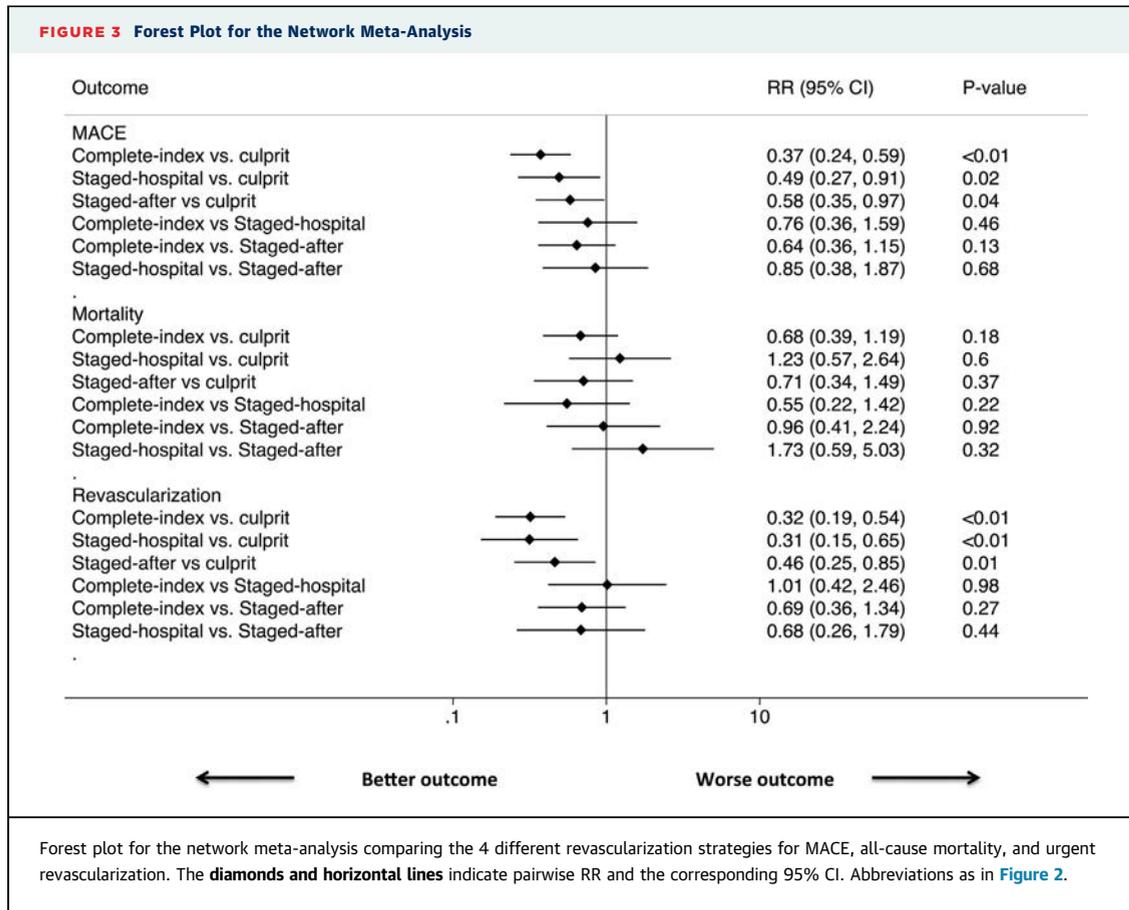


Summary plot for major adverse cardiac events, all-cause mortality, spontaneous reinfarction, and urgent revascularization in the pairwise meta-analysis. CI = confidence interval; CvLPRIT = complete versus lesion-only Primary PCI pilot study; DANAMI-3-PRIMULTI = third danish study of primary PCI in patients with ST-elevation myocardial infarction and multivessel disease: treatment of culprit lesion only or complete revascularization; HELP-AMI = HEPacoat for cuLPrIt or multivessel stenting for acute myocardial infarction; MACE = major adverse cardiac event(s); PRAMI = preventive angioplasty in acute myocardial infarction; RR = risk ratio.

**TABLE 2** Summary Estimates for the Outcomes in the Pairwise Meta-Analysis

Outcome	Incidence Complete/ Culprit-Only, %/%	Risk Ratio	95% Confidence Interval	p Value	I <sup>2</sup> , %
Major adverse cardiac events	14.6/24.4	0.57	0.42-0.77	<0.0001	57
All-cause mortality	4.6/5.8	0.76	0.52-1.12	0.17	2
Spontaneous reinfarction	3.1/5.5	0.54	0.23-1.27	0.16	47
Urgent revascularization	9.0/18.6	0.44	0.30-0.66	<0.0001	56

In an earlier network meta-analysis of 18 studies comparing the 3 different strategies (i.e., complete revascularization at the index procedure, staged procedure, or culprit-only), the authors concluded that complete revascularization as a staged procedure was associated with the lowest risk of short- and long-term mortality (33). These findings were consistent with a more recent network meta-analysis of 32 studies comparing the same revascularization strategies (34). However, a



significant limitation of both analyses was the inclusion of observational studies (15 of 18 studies in the former, and 25 of 32 studies in the latter) (33,34). There have been concerns on how these observational studies evaluated biases, particularly immortal time bias and selection bias (35). Moreover, these observational studies tended to allocate the higher-risk patients (i.e., higher Killip class or those with cardiogenic shock) to a complete revascularization at the index procedure strategy, thus the risk of mortality was increased with complete revascularization at the index procedure among these studies (36). In addition, there has been a remarkable variation in the time when the staged procedure was performed in these studies (ranging from during the index hospitalization up to 60 days after discharge) (33,34). In our analysis, we aimed to overcome these shortcomings by analyzing only randomized trials, which in turn excluded higher-risk patients (i.e., those with cardiogenic shock), and by categorizing the staged group according to the timing of the procedure (i.e., during the hospitalization vs. after discharge). By doing so, we

demonstrated that there was no difference among the 4 different strategies on hard outcomes (i.e., all-cause mortality and spontaneous reinfarction), and the risk of MACE was reduced, due to a reduction in the risk of urgent revascularization, with a complete revascularization strategy either at the index procedure or as a staged procedure either during the hospitalization or after discharge. It is important to highlight that the benefit of a complete revascularization strategy (either at the index procedure or as a staged procedure either during the hospitalization or after discharge) was driven only by urgent revascularization, which in turn could be subjective to both provider and patient bias because the presence of additional lesions is not blinded.

Our results are consistent with other meta-analyses of randomized trials that suggested that a complete revascularization strategy (either as at the index procedure or as a staged procedure) is associated with a reduction of MACE, only due to a reduction in the risk of urgent revascularization (10-12,37-41). However, these analyses had focused

on comparing a complete revascularization strategy (either at the index procedure or as a staged procedure) with a culprit-only revascularization strategy rather than exploring the relative benefit from complete revascularization at the time of primary PCI versus as a staged procedure. This comparison is important since complete revascularization at the time of primary PCI is different from a staged procedure from a technical and pathophysiological perspective (5,42). Moreover, each of the 3 strategies has some advantages and disadvantages (43).

Although our analysis suggested that there is a trend toward reduction in the risk of all-cause mortality with a complete revascularization strategy (either at the index procedure or as a staged procedure either during the hospitalization or after discharge), based on our results (RR: 0.76) and an event rate of 5.8% in the culprit-only revascularization arm, we estimate that 4,325 patients would be needed in each arm to achieve a 80% power for all-cause mortality reduction, which is almost 4 times the number of patients included in this meta-analysis. These findings support that future trials are required to determine the impact of a complete revascularization strategy on hard outcomes such as all-cause mortality. Two ongoing trials: COMPARE ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD; [NCT01399736](#)), which is comparing a complete revascularization strategy at the time of primary PCI versus a culprit-only revascularization strategy, and COMPLETE (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Primary PCI for STEMI; [NCT01740479](#)), which is comparing complete revascularization as a staged procedure versus a culprit-only revascularization strategy, will help to further clarify the impact of a complete revascularization on hard outcomes and the role of fractional flow reserve in these situations (44,45).

**STUDY LIMITATIONS.** First, there was a moderate degree of heterogeneity observed with MACE in the pairwise meta-analysis, which could be explained by the variable revascularization strategies (i.e., complete revascularization at the index procedure vs. as a staged procedure), the variation in MACE definition, the difference in the follow-up time, and the different type of stents used. We attempted to mitigate this by performing our analysis with a random effects model. Moreover, we performed multiple sensitivity

analyses in order to explore the heterogeneity (e.g., excluding trials that did not include urgent revascularization as part of the MACE definition, and excluding older trials). These sensitivity analyses yielded a similar treatment effect to the main analysis. Second, the number of studies reporting the safety outcomes (contrast-induced nephropathy and major bleeding) were limited; therefore, a network meta-analysis was not performed for these outcomes. Reassuringly, we had previously demonstrated that the risks of contrast-induced nephropathy and major bleeding were not increased with a complete revascularization strategy (11). Third, this meta-analysis included several small studies and relatively older studies in order to minimize the risk of publication bias. We performed sensitivity analyses excluding these trials for the outcome of MACE, which showed a similar treatment effect to the main analysis. Fourth, a network meta-analysis comparing the 4 revascularization strategies for the outcome of spontaneous reinfarction could not be performed due to the limited number of studies. Fifth, we did not analyze the outcome of cardiovascular mortality in this study due to the limited data on this outcome. Finally, lack of patient-level data precluded a full evaluation for differences in patient-level covariates (i.e., infarct size in the territory of the culprit artery) across comparisons.

## CONCLUSIONS

For patients with multivessel coronary artery disease undergoing primary PCI, current evidence from randomized trials suggests that the risk of all-cause mortality and spontaneous reinfarction is not different among the 4 various revascularization strategies. Complete revascularization at the index procedure or as a staged procedure during the hospitalization or after discharge was associated with a reduction of MACE due to reduction in urgent revascularization with no difference between these 3 strategies of complete revascularization. Future trials are needed to determine the impact of complete revascularization on the risk of all-cause mortality and spontaneous reinfarction.

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## PERSPECTIVES

**WHAT IS KNOWN?** Patients with STEMI and multivessel coronary disease undergoing primary PCI have worse prognosis. Data have been inconsistent about the optimum revascularization strategy for these patients.

**WHAT IS NEW?** Evidence from the available randomized trials demonstrate that there is no differences among the 4 revascularization strategies on hard outcomes of all-cause mortality and reinfarction. Complete revascularization (at

the index procedure, as a staged procedure during the hospitalization or after discharge) is associated with a reduction in the risk of MACE due to reduction in urgent revascularization (compared with culprit-only revascularization) with no differences among these 3 strategies.

**WHAT IS NEXT?** Future trials need to focus on the benefit of a complete revascularization approach in reducing the risk of mortality and reinfarction.

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**KEY WORDS** meta-analysis, myocardial infarction, percutaneous coronary intervention

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**APPENDIX** For supplemental tables, please see the online version of this article.