

Metaanalysis of Multivessel vs Culprit Artery Only Percutaneous Coronary Intervention in ST Elevation Myocardial Infarction

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Background: Primary percutaneous coronary intervention (PCI) is the most frequently used treatment modality for patients presenting with ST elevation myocardial infarction (STEMI). Current professional society guidelines recommend culprit artery only PCI. Recent evidence suggests the potential benefit of multivessel PCI among patients with STEMI that is not complicated by cardiogenic shock.

Methods: We systematically searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for clinical studies of patients with STEMI, not complicated by cardiogenic shock, who underwent primary PCI between January 1966 and January 2018. We evaluated all-cause and cardiovascular mortality, reinfarction, and repeat revascularization among patients randomized to a multivessel PCI strategy compared to a culprit artery only PCI strategy.

Results: Four randomized clinical trials with a total of 1,044 patients met the inclusion criteria. Five hundred and sixty-six patients underwent multivessel PCI, and 478 patients underwent culprit artery only PCI. Multivessel PCI reduced all the studied endpoints: total death, cardiac death, reinfarction, and repeat revascularization (all *P* values <0.05).

Conclusion: To our knowledge, this is the largest metaanalysis of randomized controlled trials studying multivessel PCI vs culprit artery only PCI in STEMI patients without shock, among whom lesion severity was graded by angiography alone. We found that compared to culprit artery only PCI, the multivessel PCI strategy was beneficial in reducing all-cause and cardiovascular mortality, reinfarction, and the need for repeat revascularization.

Keywords: Coronary artery disease, mortality, myocardial revascularization, percutaneous coronary intervention, ST elevation myocardial infarction

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INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the dominant treatment paradigm for acute ST elevation myocardial infarction (STEMI).^{1,2} Multivessel disease with stenosis in non-infarct-related arteries has been reported in as many as 40% of STEMI patients.³ Furthermore, multivessel coronary artery disease (CAD) at the time of STEMI portends a worse prognosis compared to single-vessel disease.⁴⁻⁶ Two PCI treatment options exist for these patients: (1) treatment of the culprit artery only or (2) multivessel PCI either at the time of primary PCI or in a staged manner.

The clinical rationale for focusing only on reperfusion of the infarct-related artery is to avoid the potential harm from complications that embarrass perfusion to another coronary distribution, thereby compounding the hemodynamic insult of the STEMI. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) and the 2012 European Society of Cardiology (ESC) guidelines give a Level III recommendation (do not do) for PCI of non-infarct-related coronary arteries at the time of primary PCI, outside the setting of cardiogenic shock.^{1,7} The basis for these recommendations is registry data,⁸ post-hoc analysis,⁹ and one metaanalysis.¹⁰ The conclusions of that metaanalysis

were largely driven by retrospective data.^{6,8,9,11-21} Later registry²² (2012) and metaanalysis²³ (2013) data support the benefit of multivessel PCI compared to culprit artery only PCI. The data from randomized controlled trials (RCTs) is limited.

The Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial²⁴ is the largest RCT published to date (2013) that compares culprit artery only PCI and multivessel PCI in patients with multivessel CAD who do not have cardiogenic shock. Despite being the largest RCT to study this topic, each arm of the PRAMI trial included fewer than 250 patients. The more recent Complete Versus Lesion-Only Primary PCI Trial (CvLPRIT)^{25,26} (2013, 2015) had 150 or fewer patients per arm. We performed a systematic review and metaanalysis to evaluate all published RCT data regarding culprit artery only vs multivessel PCI in STEMI patients without cardiogenic shock.

METHODS

Search Strategy

We systematically searched PubMed, Cochrane Central Register of Controlled Trials, and American and European Cardiology Scientific Sessions for clinical studies of STEMI patients undergoing PCI from January 1966 to January 2018. The following medical subject heading terms were included for a MEDLINE search and adapted for other databases as needed: (“angioplasty” OR “transluminal”) AND (“percutaneous coronary”) AND (“myocardial infarct” OR “coronary artery disease”) AND (“multivessel disease”). In addition to searching databases, we manually searched reference lists of all included studies, metaanalyses, and reviews with no language restrictions. Included studies had to be prospective RCTs comparing culprit artery only PCI with angiography-guided multivessel PCI in patients who presented with STEMI and underwent PCI. Excluded clinical studies were those that (1) used only one strategy of intervention, (2) did not specify the strategy being used, (3) did not report a comparison among strategies used, (4) did not report the outcomes of interest, or (5) included patients with cardiogenic shock or patients who underwent coronary artery bypass graft (CABG).

Data Extraction

Trial analysis, data extraction, and quality assessment were independently completed by 4 authors (D.C.G., R.N.C., F.Y.B.M., and G.E.E.) initially. These data were then further examined by a senior investigator (A.M.B.) who reviewed the trials to ensure that they met the predefined inclusion/exclusion criteria. Cases of disagreement were resolved by either a general consensus vote and/or by the senior author of the study (R.A.G.P.).

Selection Criteria

We performed an objective assessment of the studies using the method specified in the *Cochrane Handbook for Systematic Reviews of Interventions*²⁷ assessing for randomization, concealment, blinding, intention to treat, baseline comparisons, concomitant interventions, and completeness of follow-up. Our primary outcomes were defined as long-term (12-34 months) cardiac death and all-cause mortality. Our secondary outcomes were reinfarction and repeat revascularization (either another unplanned PCI or CABG).

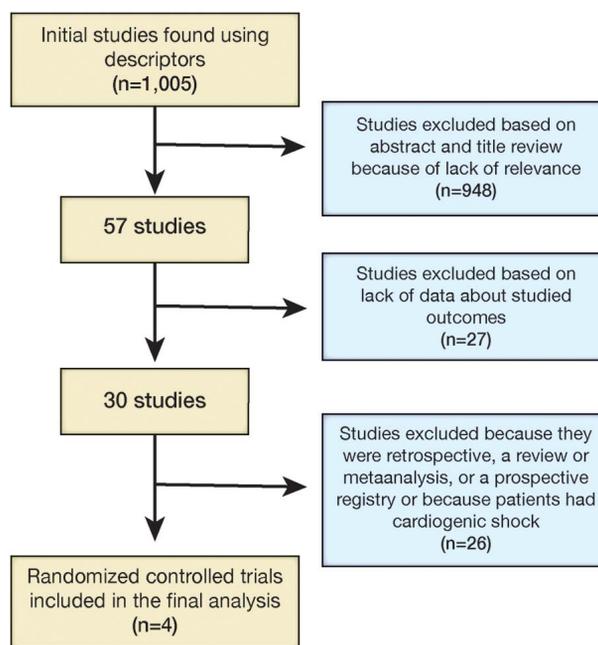


Figure 1. Process of study selection for metaanalysis.

When a multivessel PCI strategy was reported as immediate and staged procedures, we combined the groups.

Statistical Analysis

Metaanalysis was performed according to recommendations of the Cochrane Collaboration and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁸ Pooled treatment effects were estimated using odds ratio (OR) with the Mantel-Haenszel method. In concurrence with the *Cochrane Handbook of Systematic Reviews of Interventions*, the I^2 test was used for calculating heterogeneity between studies. When I^2 was up to 25% with a P value of at least 0.10, we assumed the studies were of low heterogeneity, and therefore used the fixed effects model for outcomes analysis. Otherwise, we used the random effects model. We assessed quality for each included trial. For statistical analysis, we used Review Manager v.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Study Selection

Our MEDLINE search yielded 1,004 studies. After elimination of duplicate results, the Cochrane registries did not yield additional studies, and the review of cardiology scientific sessions added one study for a total of 1,005. After a review of the titles and abstracts, 948 studies were rejected because of lack of relevance. The remaining studies were reviewed and assessed for eligibility based on the inclusion and exclusion criteria. Four studies^{24,25,29,30} were identified that met the predefined criteria for this analysis (Figure 1).

Baseline Characteristics

The pooled data provided a total of 1,044 patients undergoing multivessel PCI, with 566 patients in the multivessel

Table 1. Characteristics of the Studies Included in This Metaanalysis

Study	Inclusion Criteria	Exclusion Criteria	Follow-up, months
Di Mario et al, ²⁹ 2004	Chest pain <12 hours STEMI per AHA/ACC guidelines Maximum 3 diseased vessels	Cardiogenic shock or need for vasopressors or balloon counterpulsation Left main disease Lesions in previously treated vessels Recent thrombolysis Single-vessel disease Diffuse calcified or severe tortuosity lesion Side branch >2.0 mm requiring a stent	12
Politi et al, ³⁰ 2010	Chest pain <12 hours STEMI per AHA/ACC guidelines	Cardiogenic shock Left main disease Previous CABG Valvular disease Unsuccessful procedures	30 ± 17
Wald et al, ²⁴ 2013	STEMI per AHA/ACC guidelines Successfully treated artery >50% stenosis in non-infarct-related artery Treatable stenosis by PCI	Cardiogenic shock Left main disease or equivalent Previous CABG Unable to provide consent Chronic total occlusion	23
Gershlick et al, ²⁵ 2015	Suspected or proven STEMI Chest pain <12 hours Infarct-related artery plus at least one non-infarct-related epicardial artery >2 mm with at least one lesion >70% diameter stenosis in one plane or >50% in two planes	Any exclusion criteria for primary PCI <18 years of age Clear indication for or contraindication to multivessel primary PCI according to operator judgment Previous Q wave myocardial infarction Previous CABG Cardiogenic shock Ventricular septal defect or moderate/severe mitral regurgitation Chronic kidney disease (creatinine >200 µmol/L or estimated glomerular filtration rate <30 mL/min/1.73m ²) Suspected or confirmed thrombosis of a previously stented artery Only significant non-infarct-related artery lesion is a chronic total occlusion	12

Note: AHA/ACC guidelines require at least 1 mm in two or more contiguous limb electrocardiographic leads or 2 mm in precordial leads. Cardiogenic shock is defined as systolic blood pressure <90 mmHg or heart rate >100 bpm. Left main disease is defined as >50% ostial stenosis, unsuccessful procedures, absence of residual stenosis <30%, and/or TIMI flow grade III.

ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

PCI group and 478 patients in the culprit artery only PCI group. Table 1 summarizes the characteristics of the studies included in this metaanalysis. Patients' baseline characteristics are listed in Table 2, and interventional characteristics are listed in Table 3.

Primary Outcomes

All-cause and cardiac mortality are presented in Figures 2 and 3. In the pooled population, 25 patients (4.4%) treated with multivessel PCI and 36 patients (7.5%) treated with culprit artery only PCI did not survive during the 12- to 34-month follow-up (risk ratio [RR] 0.56, 95% confidence interval [CI] 0.34-0.92, $P=0.02$). The cardiac death analysis revealed 12

(2.1%) deaths in the multivessel PCI group and 23 (4.8%) in the culprit artery only PCI group (RR 0.40, 95% CI 0.20-0.80, $P=0.009$). All the studies were deemed to be of low heterogeneity by I^2 . Therefore, fixed effects analysis was applied.

Secondary Outcomes

The secondary outcomes of reinfarction and revascularization are presented in Figures 4 and 5, respectively. We found a significant reduction in reinfarction (RR 0.34, 95% CI 0.18-0.65, $P=0.001$) (Figure 4) and the need for repeat revascularization in the patients who underwent multivessel PCI (RR 0.38, 95% CI 0.27-0.53, $P<0.00001$).

Table 2. Baseline Characteristics of the Patients Included in This Metaanalysis

Study	Procedure	Mean Age, years \pm SD	Male Sex, n (%)	Diabetes, n (%)	Hypertension, n (%)	Anterior Infarct, n (%)
Di Mario et al, ²⁹ 2004	Multivessel n=52	63.5 \pm 12.4	46 (88.5)	21 (40.4)	30 (57.7)	27 (51.9)
	Culprit n=17	65.3 \pm 7.4	14 (82.4)	2 (11.8)	6 (35.3)	10 (58.8)
Politi et al, ³⁰ 2010	Multivessel n=65	64.5 \pm 11.7	50 (76.9)	9 (13.8)	32 (49.2)	31 (47.7)
	Culprit n=84	66.5 \pm 13.2	64 (76.2)	20 (23.8)	50 (59.5)	35 (41.7)
	Staged multivessel n=65	64.1 \pm 11.1	52 (80.0)	12 (18.5)	42 (64.6)	28 (43.1)
Wald et al, ²⁴ 2013	Multivessel n=234	62 \pm 30	177 (75.6)	35 (15.0)	94 (40.2)	67 (28.6)
	Culprit n=231	62 \pm 28	186 (80.5)	48 (20.8)	93 (40.3)	89 (38.5)
Gershlick et al, ²⁵ 2015	Multivessel n=150	64.6 \pm 11.2	128 (85.3)	19 (12.7)	54 (36.0)	54 (36.0)
	Culprit n=146	65.3 \pm 11.9	112 (76.7)	20 (13.7)	51 (34.9)	52 (35.6)

Table 3. Interventional Characteristics in the Studies Included in This Metaanalysis

Study	Drug-Eluting Stent Use	Time for Secondary Procedure, days	Medical Treatment	Follow-up, months
Di Mario et al, ²⁹ 2004	None; all heparin-coated Bx Velocity stents (Cordis Corporation, Cardinal Health)	Not specified	Aspirin Clopidogrel or ticlopidine	12
Politi et al, ³⁰ 2010	Infarct artery: 10 (11.9%) in the culprit artery only group 5 (7.7%) in the multivessel group 6 (9.2%) in the staged multivessel group	42.3 \pm 22.8	Aspirin Statin Clopidogrel for 30 days if bare metal stent or 1 year if drug-eluting stent	30 \pm 17
Wald et al, ²⁴ 2013	Infarct artery: 147 (62.8%) in the multivessel group 135 (58.4%) in the culprit artery only group Non-infarct-related artery: 165 (70.5%) in the multivessel group	40	Aspirin Clopidogrel, prasugrel, or ticagrelor Statin Beta blocker Angiotensin-converting enzyme inhibitor	23
Gershlick et al, ²⁵ 2015	141 (94.0%) in the multivessel group 127 (87.0%) in culprit artery only group	Not specified	Aspirin Clopidogrel, prasugrel, or ticagrelor Statin Beta blocker Angiotensin-converting enzyme inhibitor	12

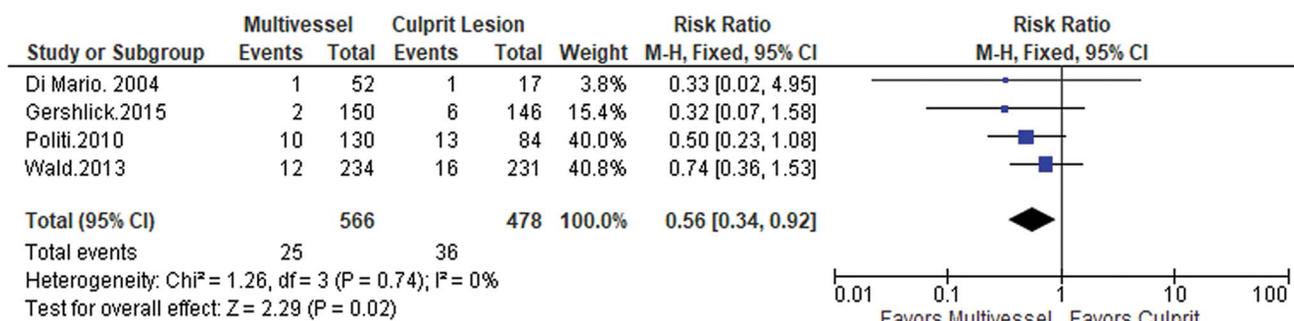


Figure 2. All-cause mortality. Multivessel percutaneous coronary intervention (PCI) strategy vs culprit artery only PCI strategy. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

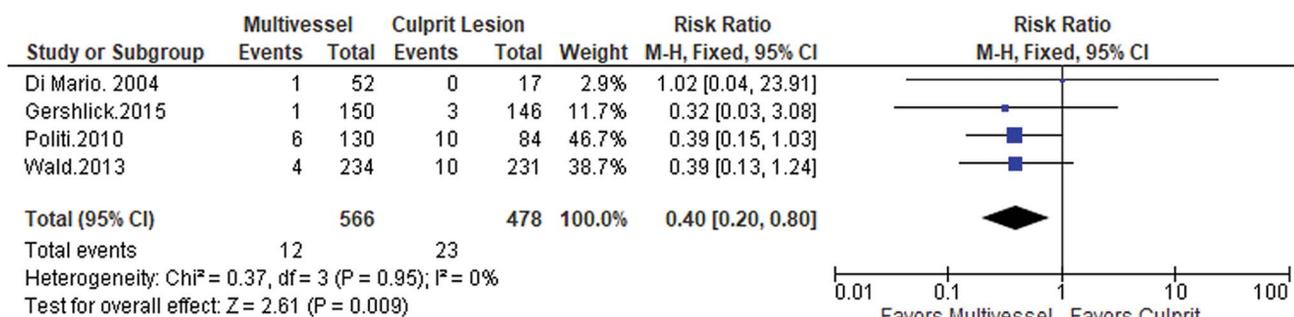


Figure 3. Cardiac mortality. Multivessel percutaneous coronary intervention (PCI) strategy vs culprit artery only PCI strategy. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

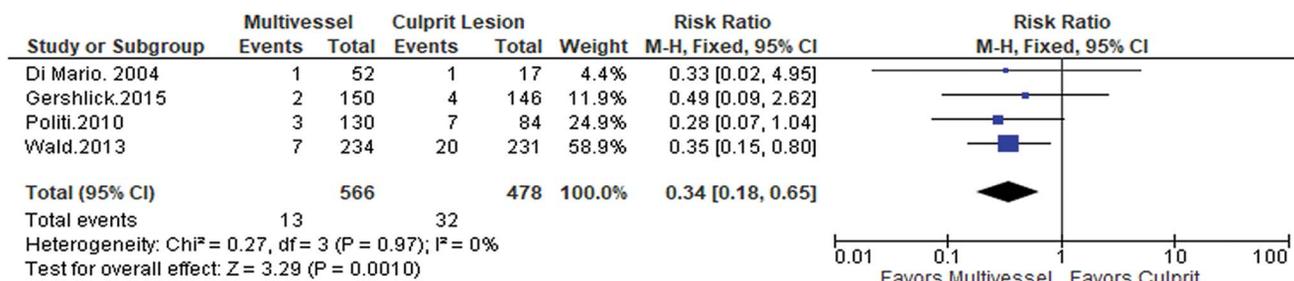


Figure 4. Reinfarction. Multivessel percutaneous coronary intervention (PCI) strategy vs culprit artery only PCI strategy. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

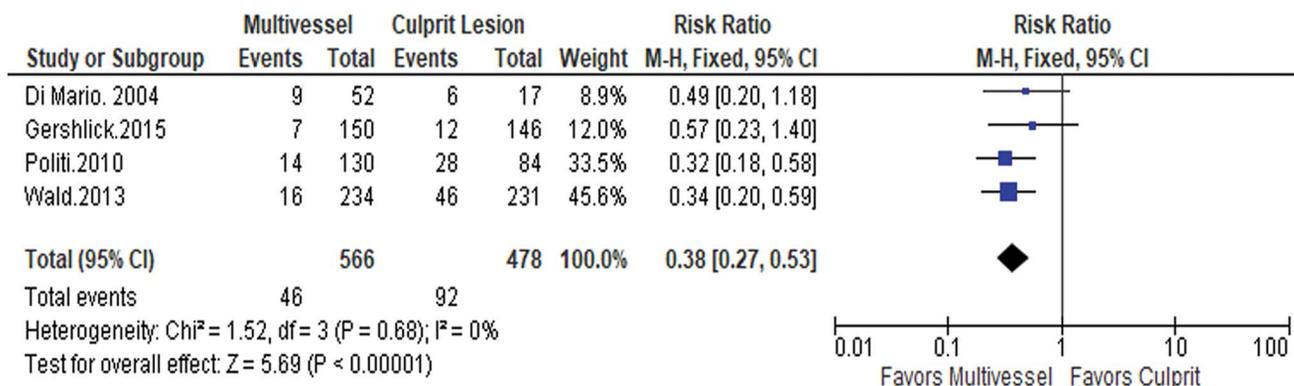


Figure 5. Repeat revascularization. Multivessel percutaneous coronary intervention (PCI) strategy vs culprit artery only PCI strategy. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

DISCUSSION

To our knowledge, this metaanalysis represents the largest pool of data from RCTs designed to compare culprit artery only PCI vs multivessel PCI revascularization in STEMI patients without cardiogenic shock. The strength of this methodology is avoidance of potential selection and operator biases that plague retrospective studies. The largest previously published metaanalysis of culprit artery only PCI vs multivessel PCI¹⁰ included 18 studies, 3 of which were RCTs, 14 were retrospective studies, and 1 was a prospective nonrandomized study. Importantly, only 2 of the 3 RCTs reported clinical outcomes beyond ejection fraction. Data from the metaanalysis demonstrated superiority of culprit artery only PCI vs multivessel PCI. However, staged PCI was superior to culprit artery only PCI. In this context, staged PCI refers to performing complete revascularization in a stepwise manner over time as opposed to at the time of primary PCI. The conclusion that culprit artery only PCI was superior to multivessel PCI was driven by data derived from retrospective studies. Three other metaanalyses that included non-RCT data demonstrated that multivessel PCI during STEMI was not deleterious.³¹⁻³³ This difference might be explained by patient selection bias in nonrandomized studies. In 2013, two metaanalyses with contradictory results were published, raising again the possibility of selection bias in non-RCT data.^{23,34} Our data could successfully add 761 patients from RCTs to the prior 283 in previously published metaanalyses, enhancing the discussion about the clinical importance of multivessel PCI in 2019.

Selection bias is likely among nonrandomized studies, especially in retrospective analyses of culprit artery only PCI vs multivessel PCI among STEMI patients performed when the ACC/AHA and ESC guidelines recommend culprit artery only PCI for STEMI patients who are not in cardiogenic shock. If an operator performed multivessel PCI in a patient without shock, one might speculate that the operator was concerned about impending cardiogenic shock or impending non-infarct-related artery vessel closure. Such a patient, in theory, should be at higher risk for cardiac events than a hemodynamically stable patient with high-grade stenosis or occlusion of only the culprit artery responsible for the STEMI. In both of the aforementioned 2013 metaanalyses, it is worth noting that low mortality rates were encountered in the culprit artery only PCI as well as the multivessel PCI groups. Since 1999, PCI techniques with stents have improved; more operators are routinely performing primary PCI for STEMI, and more patients with STEMI are receiving culprit artery revascularization with door-to-balloon times <90 minutes. All of these factors have likely contributed to lower STEMI mortality. Despite these advances, multivessel PCI significantly further decreased the mortality rate compared to culprit artery PCI alone. The patients included in the analyzed trials had either normal or reduced left ventricular ejection fractions but were only excluded from the trials if they presented with clinical signs of cardiogenic shock.

If complete revascularization is to be performed, then coronary stenosis severity must be assessed. Traditionally, coronary stenosis severity has been defined anatomically by angiographic appearance. The studies included in this metaanalysis all defined coronary stenosis sever-

ity anatomically by angiography appearance. An alternative, more recently developed method for defining coronary stenosis severity is with physiologic assessment using fractional flow reserve (FFR). However, FFR is not universally available in cardiac catheterization laboratories in 2019. Several clinical studies have suggested superior outcomes in patients without STEMI who undergo coronary revascularization based on FFR measurements rather than anatomic assessment of lesion severity. The PRIMULTI study randomized patients to culprit artery only treatment or FFR-guided complete revascularization.³⁵ Patients who received FFR-guided complete revascularization had a lower incidence of the combined endpoint of all-cause mortality, nonfatal reinfarction, and ischemia-driven reinfarction. Similarly, an RCT from Zhang et al used FFR and physiologic ischemia testing to guide complete revascularization.³⁶ The study also demonstrated better outcomes in patients who received multivessel PCI based on physiologic evaluation of coronary stenosis severity.

Two of the 4 RCTs analyzed in our metaanalysis did not demonstrate statistical superiority of a multivessel PCI strategy vs culprit artery only PCI. The HELP AMI trial (Di Mario et al) was a small study;²⁹ 69 patients were enrolled, of whom 52 were randomized to multivessel PCI. Furthermore, drug-eluting stents were not used. Interestingly, this study found the 1-year cost was similar regardless of revascularization strategy. Politi et al compared 3 groups.³⁰ Eighty-four patients were assigned to culprit artery only PCI, and 130 patients underwent a multivessel strategy. Of those 130 patients, 65 patients were assigned to complete revascularization at the time of primary PCI for STEMI and another 65 patients were assigned to staged revascularization.

The largest RCT comparing culprit artery only PCI vs multivessel PCI is PRAMI²⁴ (Wald et al) in which 231 patients were randomized to a culprit artery only PCI strategy and 234 patients were assigned to a multivessel PCI strategy. The trial was powered to detect a 30% reduction in major adverse cardiac events among the complete revascularization group, assuming a 20% annual rate of the primary outcome. The primary outcome was defined as a composite of cardiac death, nonfatal myocardial infarction, and refractory angina. The data and safety monitoring committee stopped the trial at 23 months. During that follow-up period, 53 patients in the culprit artery only PCI group and 21 patients in the multivessel PCI group reached the primary endpoint, providing a calculated hazard ratio of 0.35 for complete revascularization (95% CI 0.21-0.58, $P < 0.001$). Of note, a criticism of this trial is that the stenosis threshold for stenting a non-infarct-related vessel was 50%.³⁷ CvLPRIT is the most recent study (2015) and included 146 patients in the culprit artery only PCI group and 150 patients in the multivessel PCI group.²⁵ The PCI threshold was angiographic stenosis of 70% in one view or 50% in two views. The results were very similar to PRAMI. The combination of the last two studies led the ACC to revoke its American Board of Internal Medicine (ABIM) Choosing Wisely recommendation³⁷ against performing multivessel PCI at the time of primary PCI for STEMI. However, the ACC has yet to strongly recommend the multivessel PCI approach.

The findings of our metaanalysis, which include only RCTs, are hypothesis generating. Our analysis suggests an important advantage of a multivessel PCI strategy vs a culprit artery only PCI strategy for all prespecified clinical endpoints including all-cause mortality. The retraction of the ABIM Choosing Wisely recommendation against multivessel PCI is a positive response to trials analyzed in this study. Further, the 2015 ACC/AHA update to the primary PCI guidelines for STEMI gave complete revascularization a Level IIIb recommendation.³⁸

Limitations

This analysis is limited in that the total number of patients is still small. Insufficient data are available to compare culprit artery only PCI vs staged PCI, and the follow-up time was variable, ranging from 12 months to 34 months. Data for in-hospital or short-term outcomes were not always available. Some procedural complications (such as contrast-induced nephropathy and bleeding complications), as well as length of hospital stay, were not included in this analysis. These outcomes were not homogeneously reported in all studies. To avoid analysis bias, they were excluded.

CONCLUSION

This metaanalysis demonstrates that a strategy of multivessel PCI with complete revascularization is significantly superior to culprit artery only primary PCI in patients with STEMI not complicated by cardiogenic shock. If complete revascularization is to be performed, then the issue of whether anatomic assessment or physiologic assessment should guide revascularization needs to be addressed. Further, multicenter RCTs are needed to address the issue of whether staged PCI for non-infarct-related arteries is superior to culprit artery only PCI or complete revascularization at the time of STEMI. In fact, the results of the ongoing COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trial (NCT01740479) in which STEMI patients are randomized to culprit artery only or staged complete revascularization are eagerly awaited. The time for incorporation of these results into clinical guidelines may be near.

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