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Multivessel Versus Culprit-Only Revascularization in STEMI and Multivessel Coronary Artery Disease

Meta-Analysis of Randomized Trials

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ABSTRACT

OBJECTIVES The goal of this systematic review and meta-analysis was to provide a comprehensive evaluation of contemporary randomized trials addressing the efficacy and safety of multivessel versus culprit vessel-only percutaneous coronary intervention (PCI) among patients presenting with ST-segment elevation myocardial infarction and multivessel coronary artery disease.

BACKGROUND Multivessel coronary artery disease is present in about one-half of patients with ST-segment elevation myocardial infarction. Randomized controlled trials comparing multivessel and culprit vessel-only PCI produced conflicting results regarding the benefits of a multivessel PCI strategy.

METHODS A comprehensive search for published randomized controlled trials comparing multivessel PCI with culprit vessel-only PCI was conducted on ClinicalTrials.gov, PubMed, Web of Science, EBSCO Services, the Cochrane Central Register of Controlled Trials, Google Scholar, and scientific conference sessions from inception to September 15, 2019. A meta-analysis was performed using a random-effects model to calculate the risk ratio (RR) and 95% confidence interval (CI). Primary efficacy outcomes were all-cause mortality and reinfarction.

RESULTS Ten randomized controlled trials were included, representing 7,030 patients: 3,426 underwent multivessel PCI and 3,604 received culprit vessel-only PCI. Compared with culprit vessel-only PCI, multivessel PCI was associated with no significant difference in all-cause mortality (RR: 0.85; 95% CI: 0.68 to 1.05) and lower risk for reinfarction (RR: 0.69; 95% CI: 0.50 to 0.95), cardiovascular mortality (RR: 0.71; 95% CI: 0.50 to 1.00), and repeat revascularization (RR: 0.34; 95% CI: 0.25 to 0.44). Major bleeding (RR: 0.92; 95% CI: 0.50 to 1.67), stroke (RR: 1.15; 95% CI: 0.65 to 2.01), and contrast-induced nephropathy (RR: 1.25; 95% CI: 0.80 to 1.95) were not significantly different between the 2 groups.

CONCLUSIONS Multivessel PCI was associated with a lower risk for reinfarction, without any difference in all-cause mortality, compared with culprit vessel-only PCI in patients with ST-segment elevation myocardial infarction.
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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CI = confidence interval

CIN = contrast-induced nephropathy

FFR = fractional flow reserve

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

RR = risk ratio

STEMI = ST-segment elevation myocardial infarction

Approximately 50% of patients presenting with ST-segment elevation myocardial infarction (STEMI) have at least 1 other obstructive lesion (>50% stenosis) in a nonculprit vessel at index presentation besides the culprit lesion undergoing primary percutaneous coronary intervention (PCI) (1-3). The presence of obstructive lesions in nonculprit coronary vessels is associated with worse short- and long-term outcomes (4). Whether these nonculprit lesions need revascularization has been controversial (5). Previous guideline recommendations advised against nonculprit vessel PCI in the absence of spontaneous myocardial ischemia or intermediate- or high-risk findings on invasive testing (6). Following data showing the benefit of multivessel revascularization in stable coronary artery disease (CAD) (7), and

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several subsequent randomized controlled trials (RCTs) showing improved outcomes in patients with STEMI undergoing multivessel revascularization (8-16), the American professional medical societies updated their guidelines recommending PCI of the noninfarct artery to be considered in selected patients (17). However, the contemporary European guidelines recommend routine revascularization of the nonculprit vessel prior to hospital discharge (Class IIa recommendation) (18). Most of the benefit observed in RCTs was due to a reduction in repeat revascularization. The recent results of the COMPLETE (Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI) trial, a multinational RCT of 4,041 patients, showed that a strategy of complete revascularization significantly reduced the risk for cardiovascular death or myocardial infarction (MI) compared with culprit lesion-only PCI (19). However, the COMPLETE trial was not powered to detect true differences in all-cause mortality between the 2 treatment strategies.

The goal of this systematic review and meta-analysis was to provide a comprehensive evaluation of contemporary randomized trials addressing the efficacy and safety of multivessel versus culprit vessel-only PCI among patients presenting with STEMI and multivessel CAD.

METHODS

SEARCH STRATEGY. The systematic review and meta-analysis was performed according to the

research grants for Abiomed and Chiesi. Dr. Mena-Hurtado is a consultant for Cook Medical, Medtronic, Cardinal Health, and Boston Scientific. Dr. Abbott has received research grants with no direct compensation from Abbott Vascular, Sinomed, AstraZeneca, Bristol-Myers Squibb, and Biosensors Research USA. Dr. Bhatt is an advisory board member for Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, and Regado Biosciences; is on the boards of directors of the Boston VA Research Institute, the Society of Cardiovascular Patient Care, and TobeSoft; is chair of the American Heart Association Quality Oversight Committee; is a member of data monitoring committees for the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), the Cleveland Clinic (including for the ExCEED trial, funded by Edwards Lifesciences), the Duke Clinical Research Institute, the Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and the Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org; vice chair, ACC Accreditation Committee), the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee, funded by Boehringer Ingelheim; AEGIS-II executive committee, funded by CSL Behring), Belvoir Publications (editor-in-chief, *Harvard Heart Letter*), the Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (editor-in-chief, *Journal of Invasive Cardiology*), the *Journal of the American College of Cardiology* (guest editor, associate editor), Medtelligence/ReachMD (continuing medical education steering committees), the Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and U.S. national coleader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), the Society of Cardiovascular Patient Care (secretary/treasurer), WebMD (continuing medical education steering committees); is deputy editor of *Clinical Cardiology*; is chair of the NCDR-ACTION Registry Steering Committee and the VA CART Research and Publications Committee; has received research funding from Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); is a site co-investigator for Biotronik, Boston Scientific, Cardiovascular Systems, St. Jude Medical (now Abbott), and Svelte; is a trustee of the American College of Cardiology; and has conducted unfunded research for FlowCo, Merck, Novo Nordisk, PLx Pharma, and Takeda. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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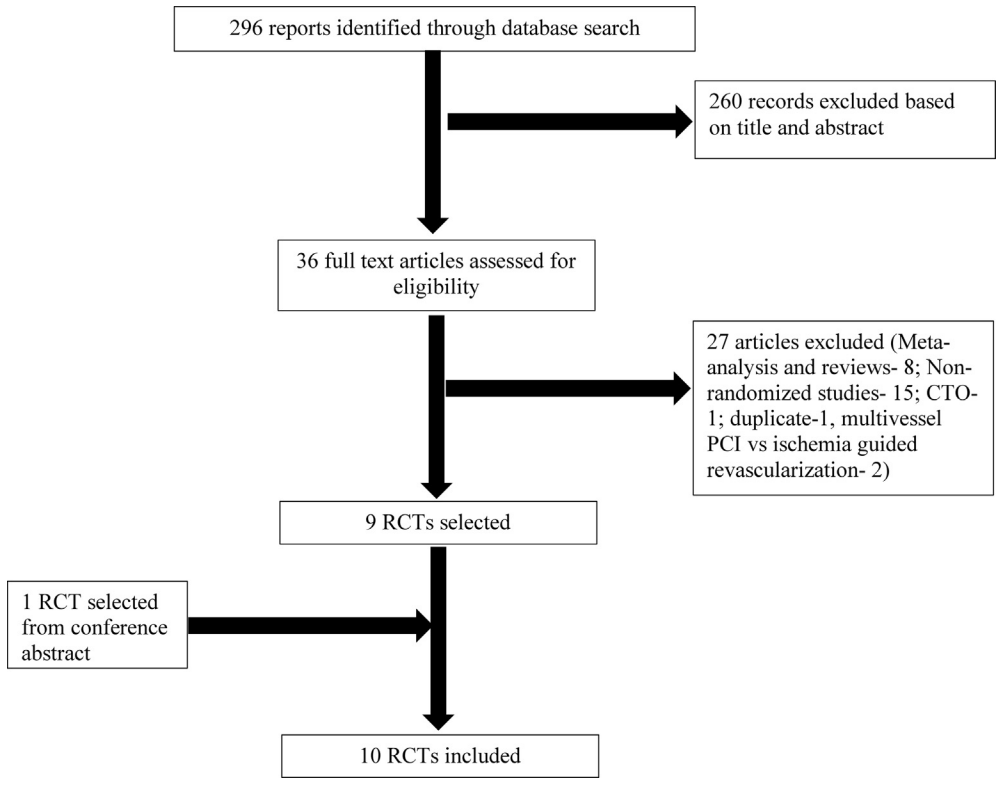
TABLE 1 Definitions of Outcomes in the Included Randomized Controlled Trials

Study (Year) (Ref. #)	Definition of Multivessel Disease	Primary Endpoint	Definition of Reinfarction	Definition of Bleeding
HELP AMI (2004) (8)	Culprit artery + 1–3 lesions in major nonculprit arteries	Repeat revascularization	NR	NR
Politi et al. (2010) (9)	>70% diameter stenosis of ≥2 coronary arteries or their major branches by visual estimation	MACE	NR	NR
Ghani et al. (2012) (10)	≥1 significant stenosis in ≥2 major coronary arteries or combination of side branch and main vessel supplying different territories	EF at 6 months	New Q waves on ECG or new CK and CK-MB increases above the ULN	NR
PRAMI (2013) (11)	Stenosis of ≥50% in ≥1 coronary artery other than culprit artery and stenosis was deemed to be treatable by PCI	Cardiovascular death, recurrent MI, refractory angina	Symptoms of cardiac ischemia and a troponin level above the 99th centile; within 14 days of randomization, new evidence on ECG of ST-segment elevation or LBBB and angiographic evidence of coronary artery occlusion	Requiring transfusion or surgery
CvLPRIT (2015) (12)	Culprit artery + ≥1 nonculprit artery with ≥1 lesion deemed angiographically significant (>70% diameter stenosis in 1 plane or >50% in 2 planes)	All-cause mortality, recurrent MI, heart failure, ischemia-driven revascularization by PCI/CABG	Type 1: recurrent angina symptoms or new changes on ECG occurring before PCI or <48 h from PCI compatible with re-MI associated with elevation of CK-MB, troponin, or total CK beyond ULN and 20% or more above the previous value Type 4a: CK-MB or total CK >3 times ULN within 48 h following PCI Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy and fulfilling criteria of spontaneous MI	Cumulative occurrence of intracranial or intraocular bleeding, hemorrhage at the vascular access site requiring intervention, a reduction in Hb level of ≥5 g/dl, reoperation for bleeding or transfusion of a blood product (≥2 U), bleeding causing substantial hypotension requiring the use of inotropic agents
DANAMI-3-PRIMULTI (2015) (13)	Angiographic diameter stenosis >50% in ≥1 nonculprit artery	All-cause mortality, recurrent MI, ischemia-driven revascularization of nonculprit artery	Typical chest pain accompanied by a substantial rise in troponins, development of new Q waves on ECG, or both	Requiring transfusion or surgery
PRAGUE-13 (2015) (14)	≥1 stenosis (≥70%) of nonculprit coronary artery by angiography, diameter of artery ≥2.5 mm	All-cause mortality, recurrent MI, stroke	NR	NR
Hamza et al. (2016) (15)	Culprit artery + ≥80% non-culprit artery stenosis by angiography	All-cause mortality, recurrent MI, and ischemia-driven revascularization	NR	Intracranial bleeding, hemorrhage associated with a drop in Hb of 5 g/dl, or fatal bleeding according to TIMI bleeding criteria
Compare-Acute (2017) (16)	Culprit artery + ≥50% non-culprit artery stenosis by angiography	All-cause mortality, nonfatal MI, any revascularization, and cerebrovascular events	NR	NR
COMPLETE (2019) (19)	One angiographically significant nonculprit lesion amenable to successful PCI and located in a vessel with a diameter ≥2.5 mm that was not stented as part of the index culprit lesion PCI	Cardiovascular death or reinfarction Cardiovascular death, reinfarction or ischemia-driven revascularization	Third universal definition of MI	Clinically overt symptomatic bleeding with ≥1 of the following criteria: • Fatal • Symptomatic intracranial hemorrhage, retroperitoneal hemorrhage • Intraocular hemorrhage leading to significant vision loss • Decrease in Hb of ≥3.0 g/dl (with each blood transfusion unit counting for 1.0 g/dl of Hb) or requiring transfusion of ≥2 U of red blood cells or equivalent of whole blood • Requiring surgical intervention to stop the bleeding

CABG = coronary artery bypass graft; CK = creatine kinase; Compare-Acute = Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD; COMPLETE = Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI; CvLPRIT = Complete Versus Lesion-Only Primary PCI Trial; DANAMI-3-PRIMULTI = Danish Study of Optimal Acute Treatment of Patients With ST-Elevation Myocardial Infarction-Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization; ECG = electrocardiography; EF = ejection fraction; Hb = hemoglobin; HELP AMI = Hepacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction; LBBB = left bundle branch block; MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; PRAGUE-13 = Multivessel Disease Diagnosed at the Time of PPCI for STEMI: Complete Revascularization Versus Conservative Strategy; PRAMI = Preventive Angioplasty in Acute Myocardial Infarction; TIMI = Thrombolysis In Myocardial Infarction; ULN = upper limit of normal.

FIGURE 1 CONSORT Diagram



Search strategy and selection of studies. CONSORT = Consolidated Standards of Reporting Trials; CTO = chronic total occlusion; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (20). The initial search strategy was developed by 2 authors (V.A. and P.V.). A systematic search, without language restriction, was performed in PubMed, EMBASE, SCOPUS, Google Scholar, and ClinicalTrials.gov from inception to September 15, 2019, for studies comparing multivessel PCI with culprit vessel-only PCI in patients with STEMI with multivessel CAD. The reference lists of original studies, conference abstracts, and relevant review papers were further reviewed. We used the following keywords: "multivessel revascularization," "multivessel percutaneous coronary intervention," "complete revascularization," "culprit vessel revascularization," "culprit vessel percutaneous coronary intervention," "target vessel revascularization," "culprit coronary artery revascularization," "infarct-related artery revascularization," "ST elevation myocardial infarction," "randomized controlled trial," "randomized trial," and "clinical trial."

STUDY SELECTION. We included studies that met the following eligibility criteria: 1) RCTs; that 2) evaluated the efficacy and safety of multivessel PCI versus culprit vessel-only PCI; in 3) patients with multivessel CAD presenting with STEMI. Studies that enrolled patients with cardiogenic shock or comparing alternative revascularization techniques were excluded.

DATA EXTRACTION. Two investigators (V.A. and P.V.) independently performed a review of published papers and screened abstracts and full-text versions of all studies that met the inclusion criteria. Any divergence was resolved through consensus.

CLINICAL OUTCOMES. We extracted the following clinical outcomes from individual trials: 1) all-cause mortality; 2) reinfarction; 3) cardiovascular mortality; 4) repeat revascularization; 5) stroke; 6) contrast-induced nephropathy (CIN); and 7) major bleeding.

The definitions of reinfarction varied across the studies, and trial-specific definitions were used (Table 1).

The primary efficacy outcomes were all-cause mortality and reinfarction. Secondary efficacy outcomes were cardiovascular mortality and repeat

TABLE 2 Characteristics of the Included RCTs

Study (Year) (Ref. #)	Study Design	Study Period	Blinding	Timing of Multivessel PCI	FFR Use and Indication in Nonculprit Artery	Follow-Up Period
HELP AMI (2004) (8)	RCT, multicenter	NR	No	Index only	No	12 months
Politi et al. (2010) (9)	RCT, single center	January 2003 to December 2007	No	Index and staged (56.8 ± 12.9 days)	No	2.5 ± 1.4 yrs
Ghani et al. (2012) (10)	RCT, single center	June 2004 to February 2007	No	Staged (in-hospital, <3 weeks)	Yes, FFR ≤0.75 or severe lesions (>90% stenosis)	36 months
PRAMI (2013) (11)	RCT, multicenter	April 2008 to January 2013	Yes (outcome assessment)	Index only	No	23 months
CvLPRIT (2015) (12)	RCT, multicenter	May 2011 to May 2013	Yes (outcome assessment)	Index and staged (in-hospital)	No	12 months
DANAMI-3-PRIMULTI (2015) (13)	RCT, multicenter	March 2011 to February 2014	Yes (outcome assessment)	Staged (2 days)	Yes, FFR ≤0.80 or severe lesions (>90% stenosis)	27 months (IQR: 12–44 months)
PRAGUE-13 (2015) (14)	RCT, multicenter	September 2008 to December 2014	NR	Staged (3–40 days)	No	38 months
Hamza et al. (2016) (15)	RCT, multicenter	June 2013 to February 2014	NR	Index and staged (<3 days)	NR	6 months
Compare-Acute (2017) (16)	RCT, multicenter	July 2011 to October 2015	No	Index and staged (<3 days)	Yes, FFR ≤0.80	12 months
COMPLETE (2019) (19)	RCT, multicenter	February 2013 to March 2017	Yes (outcome assessment)	Staged (23 days; IQR: 12.5–33.5 days)	Yes, FFR ≤0.80	36.2 months

FFR = fractional flow reserve; IQR = interquartile range; RCT = randomized controlled trial; other abbreviations as in Table 1.

revascularization. The primary safety outcome was major bleeding. The secondary safety outcomes were stroke and CIN.

STATISTICAL ANALYSES. The meta-analysis was performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) with the metafor package and Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Because of heterogeneity in the methodologies of the included studies, the risk ratios (RRs) and 95% confidence intervals (CIs) of the aforementioned outcomes were calculated using a random-effects model. Heterogeneity was assessed using Higgins and Thompson's I^2 statistic, with values of <25%, 25% to 75%, and >75% corresponding to low, moderate, and high levels of heterogeneity, respectively (21). We performed meta-regression with random effects to measure the influence of baseline characteristics on primary efficacy outcomes. Meta-regression was also used to assess the association between index multivessel PCI and effect size for all study outcomes. Publication bias was visually estimated using funnel plots. A power analysis was performed to detect a 15% meaningful difference in effect size between the groups in terms of all-cause mortality, as a primary outcome. A 2-tailed p value <0.05 was considered to indicate statistical significance. Sensitivity analysis was performed using the exclusion method with the following: 1) exclusion of studies with staged revascularization; and 2) exclusion of studies with index revascularization. The risk for bias among the included RCTs was assessed using the Cochrane risk bias assessment tool (Supplemental Table 1).

RESULTS

SEARCH RESULTS. Our search strategy yielded 296 results (**Figure 1**). After detailed evaluation, 36 full-text papers were assessed for eligibility. After exclusion of 27 papers, 9 papers including 9 RCTs were selected (8-13,15,16,19). One paper was additionally included from a conference abstract (14).

STUDY CHARACTERISTICS. This meta-analysis included 10 RCTs with 7,030 patients, of whom 3,426 were randomized to multivessel revascularization and 3,604 to culprit vessel-only revascularization. Fractional flow reserve (FFR) was used to guide multivessel PCI in 4 RCTs. The cutoff value for FFR was ≤0.80 in 3 trials (13,16,19) and ≤0.75 in 1 trial (**Table 2**) (10). The mean age of the study patients ranged from 52.2 to 66.5 years, and 80.8% were men (**Table 3**). The prevalence of hypertension and diabetes mellitus was 42.2% and 19%, respectively. The proportions of patients with 3-vessel CAD and prior MI were 28.9% and 6.8%, respectively.

TABLE 3 Baseline Characteristics of Study Populations in Individual Randomized Controlled Trials

Study (Year) (Ref. #)	Study Population (Complete/CV Only)	Mean or Median (IQR) Age (Complete/CV Only)	Male (%)	DM (%)	Hypertension (%)	Smoking, Current or Previous (%)	3-Vessel Disease (%)	Prior MI (%)	Anterior MI (%)	DES (%)	DAPT (%)
HELP AMI (2004) (8)	52/17	63.5 ± 12.4/65.3 ± 7.4	87.0	18.8	42.0	71.0	34.8	NR	53.6	NR	NR
Politi et al. (2010) (9)	130/84	64.1 ± 11.1/66.5 ± 13.2	77.5	19.1	57.9	NR	32.2	NR	44.0	9.8	CV only: 84.5 Complete: 97.0
Ghani et al. (2012) (10)	79/40	62 ± 10/61 ± 11	81.5	5.8	31.4	46.2	16.5	5.8	24.0	20.6	NR
PRAMI (2013) (11)	234/231	62 (32–92)/62 (33–90)	78.0	17.8	40.2	51.8	36.0	7.5	33.5	60.6	100
CvLPRIT (2015) (12)	150/146	64.6 (11.2)/65.3 (11.9)	81.0	13.6	36.6	30.6	22.6	4.0	35.8	93.3	CV only: 94.5 Complete: 91.0
DANAMI-3-PRIMULTI (2015) (13)	314/313	64 (37–94)/63 (34–92)	81.1	11.3	44.0	49.6	31.4	7.0	34.6	93.7	CV only: 99.0 Complete: 99.0
PRAGUE-13 (2015) (14)	106/108	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hamza et al. (2016) (15)	50/50	56.4 ± 11.5/52.2 ± 10.6	84.0	50.0	31.0	75.0	31.0	8.0	47.0	100	NR
Compare-Acute (2017) (16)	295/590	62 ± 10/61 ± 10	77.1	15.4	47.2	46.1	32.2	7.9	35.1	97.0	NR
COMPLETE (2019) (19)	2,016/2,025	61.6 ± 10.7/62.4 ± 10.7	79.8	19.5	49.7	39.7	23.4 (≥2-vessel disease)	7.4	34.3	85.0	CV only: 99.7 Complete: 99.4

CV = culprit vessel; DAPT = dual-antiplatelet therapy; DES = drug-eluting stent; DM = diabetes mellitus; IQR = interquartile range; other abbreviations as in Table 1.

Revascularization of the nonculprit vessel was performed only during the index procedure in 2 RCTs (8,11), while 3 RCTs included intention-to-treat index nonculprit vessel revascularization, although early staged procedures were performed in a minority of the trial population (12,15,16). Staged revascularization was performed in 4 RCTs (10,13,14,19). One RCT included both index and staged revascularization (50% each) (9). The timing of staged revascularization ranged from 2 days to 57 days after index PCI of the culprit vessel. The follow-up period was 25 months (interquartile range: 12 to 36 months).

POWER ANALYSIS. Following Valentine et al. (22), we conducted a power calculation for our current meta-analysis approach to detect a 15% meaningful difference in effect size between the groups for the primary endpoint of all-cause mortality. The statistical power of our analysis was 92% at a significance level of 5%.

MULTIVESSEL PCI VERSUS CULPRIT VESSEL–ONLY PCI. Primary efficacy outcomes. There was no statistically significant difference in the risk for all-cause mortality between the 2 groups (RR: 0.85; 95% CI: 0.68 to 1.05) (**Central Illustration**). Multivessel PCI was associated with a significantly lower risk for reinfarction compared with culprit vessel-only PCI (RR: 0.69; 95% CI: 0.50 to 0.95) (**Central Illustration**). Heterogeneity was low for both all-cause mortality and reinfarction.

Secondary efficacy outcomes. Compared with culprit vessel-only PCI, multivessel PCI was associated with a lower risk for cardiovascular mortality (RR: 0.71; 95% CI: 0.50 to 1.00) (**Figure 2A**) and repeat revascularization (RR: 0.34; 95% CI: 0.25 to 0.44) (**Figure 2B**). Heterogeneity was low for cardiovascular mortality and moderate for repeat revascularization.

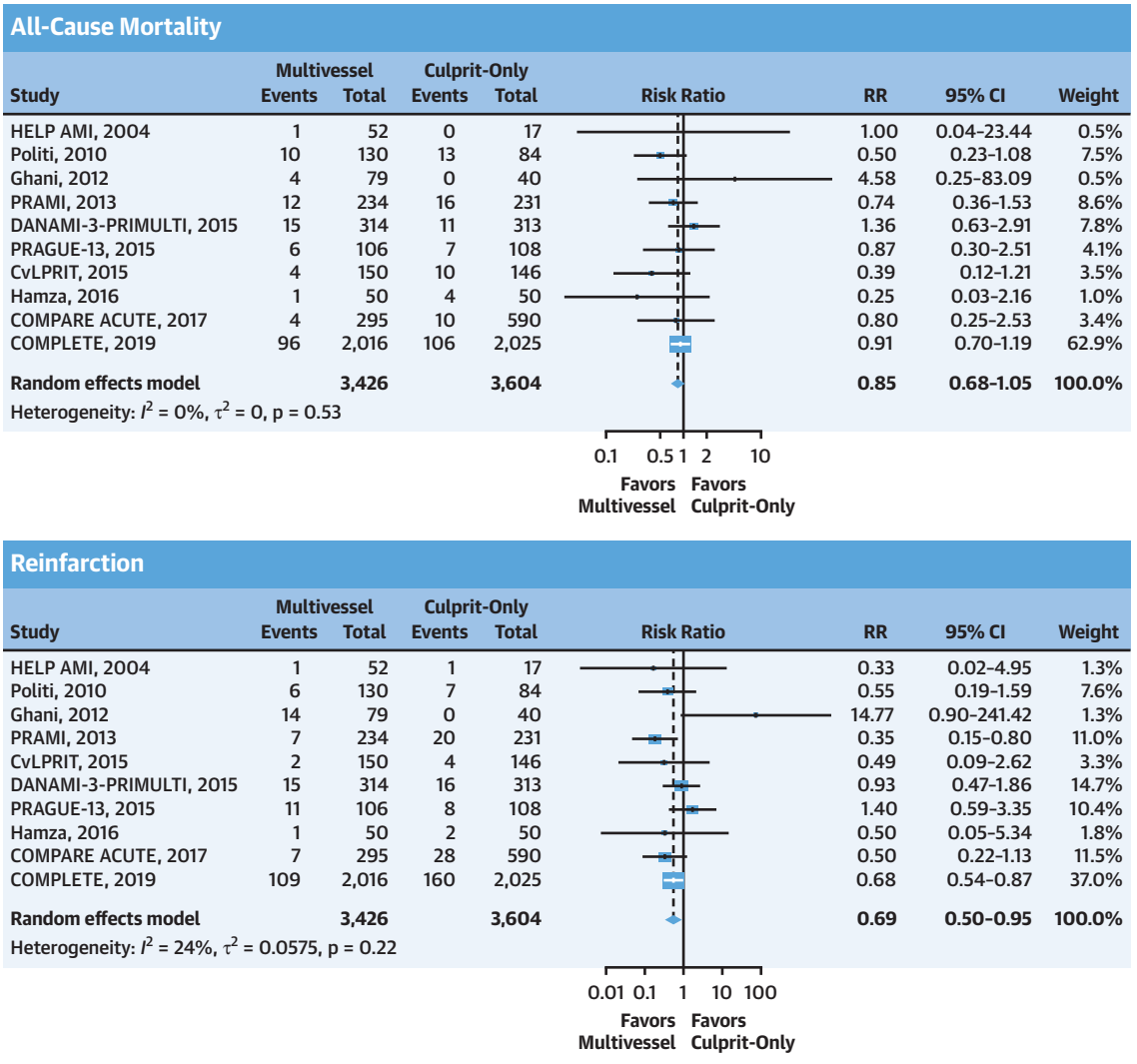
SAFETY OUTCOMES. Primary safety outcome. There was no difference in major bleeding between the 2 groups (RR: 0.92; 95% CI: 0.50 to 1.67) (**Figure 3**). Heterogeneity was moderate.

Secondary safety outcomes. There was no statistically significant difference in the risk for stroke (RR: 1.15; 95% CI: 0.65 to 2.01) or CIN between the 2 groups (RR: 1.25; 95% CI: 0.80 to 1.95) (**Figures 4A and 4B**, respectively). Heterogeneity was low for both outcomes.

META-REGRESSION. Meta-regression showed that index revascularization of the nonculprit vessel was significantly associated with reinfarction ($p = 0.03$) (Supplemental Table 2).

SENSITIVITY ANALYSIS. Pooling of RCTs that compared index multivessel PCI with culprit vessel-only PCI showed lower risk for all-cause mortality,

CENTRAL ILLUSTRATION **Primary Efficacy Outcomes**



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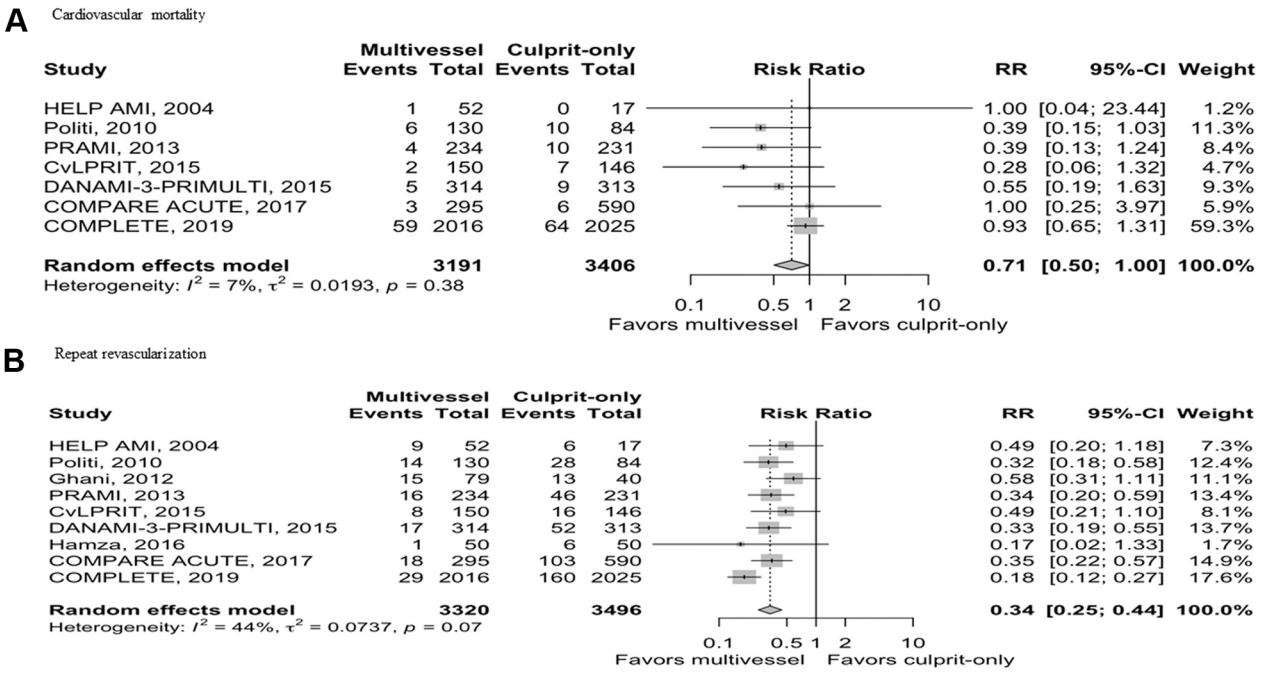
Forest plots demonstrating all-cause mortality **(top)** and reinfarction **(bottom)**. COMPARE ACUTE = Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD; COMPLETE = Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI; CvLPRIT = Complete Versus Lesion-Only Primary PCI Trial; DANAMI-3-PRIMULTI = Danish Study of Optimal Acute Treatment of Patients With ST-Elevation Myocardial Infarction-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; PRAGUE-13 = Multivessel Disease Diagnosed at the Time of PPCI for STEMI: Complete Revascularization Versus Conservative Strategy; PRAMI = Preventive Angioplasty in Acute Myocardial Infarction.

reinfarction, cardiovascular mortality, and repeat revascularization with index multivessel PCI (Supplemental Figure 1.1). Pooling of RCTs that compared staged multivessel PCI with culprit vessel-only PCI showed lower risk for repeat revascularization with a staged procedure, while no statistically significant difference was observed for all-cause mortality, reinfarction, and cardiovascular mortality (Supplemental Figure 1.2). Pooling of RCTs that compared FFR-guided multivessel PCI with culprit vessel-only PCI is demonstrated in Supplemental Figure 1.3. A funnel plot for visual inspection of publication bias is presented in Supplemental Figure 2.

FIGURE 2 Secondary Efficacy Outcomes



Forest plots demonstrating cardiovascular mortality **(A)** and repeat revascularization **(B)**.

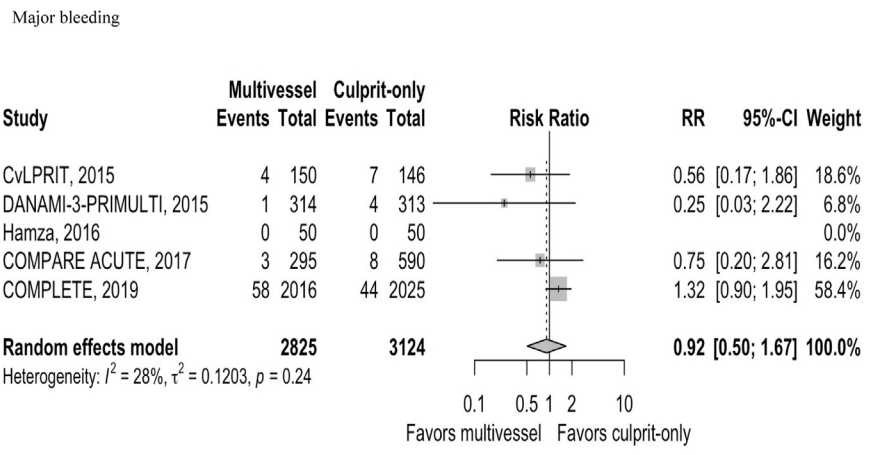
DISCUSSION

In this meta-analysis of 10 RCTs evaluating 7,030 patients presenting with STEMI and multivessel CAD randomized to multivessel PCI versus culprit vessel-only PCI, a strategy of multivessel PCI was associated with 31% lower risk for reinfarction, with no significant difference in all-cause mortality. Furthermore, there was 29% lower risk for cardiovascular mortality and 66% lower risk for repeat revascularization with multivessel PCI, without any difference in major adverse events of bleeding, stroke, or CIN.

The presence of multivessel CAD on coronary angiography at the time of STEMI has been associated with poor prognosis, including lower reperfusion success and higher risk for adverse cardiac events and mortality compared with single-vessel CAD (23). Although it is enticing to revascularize the nonculprit vessel, there is a risk for inappropriate assessment of lesion severity resulting in unnecessary interventions as well as complications. Several RCTs showed improved outcomes in patients with STEMI undergoing multivessel revascularization (8–16). Most of the benefit observed in RCTs was due to a reduction in repeat revascularization, which is not surprising (as revascularization is performed early during the disease phase), until the COMPLETE trial, a multinational RCT of 4,041 patients, showed that a strategy of multivessel revascularization was superior to culprit lesion–only PCI in reducing the risk for cardiovascular death or MI (19). Earlier meta-analyses performed prior to that trial failed to demonstrate any benefit with respect to hard clinical outcomes in multivessel PCI (24–28). There remains a discordance in guidelines endorsed by the professional medical societies, with the American College of Cardiology and American Heart Association recommending revascularization of nonculprit vessels only in selected patients (Class IIb recommendation) and the European Society of Cardiology recommending routine revascularization of nonculprit vessel (Class IIa recommendation) (17,18).

In the present meta-analysis, we found that multivessel PCI in patients with STEMI was associated with nearly 30% lower risk for both cardiovascular death and reinfarction compared with culprit vessel-

FIGURE 3 Primary Safety Outcome



Forest plot demonstrating major bleeding.

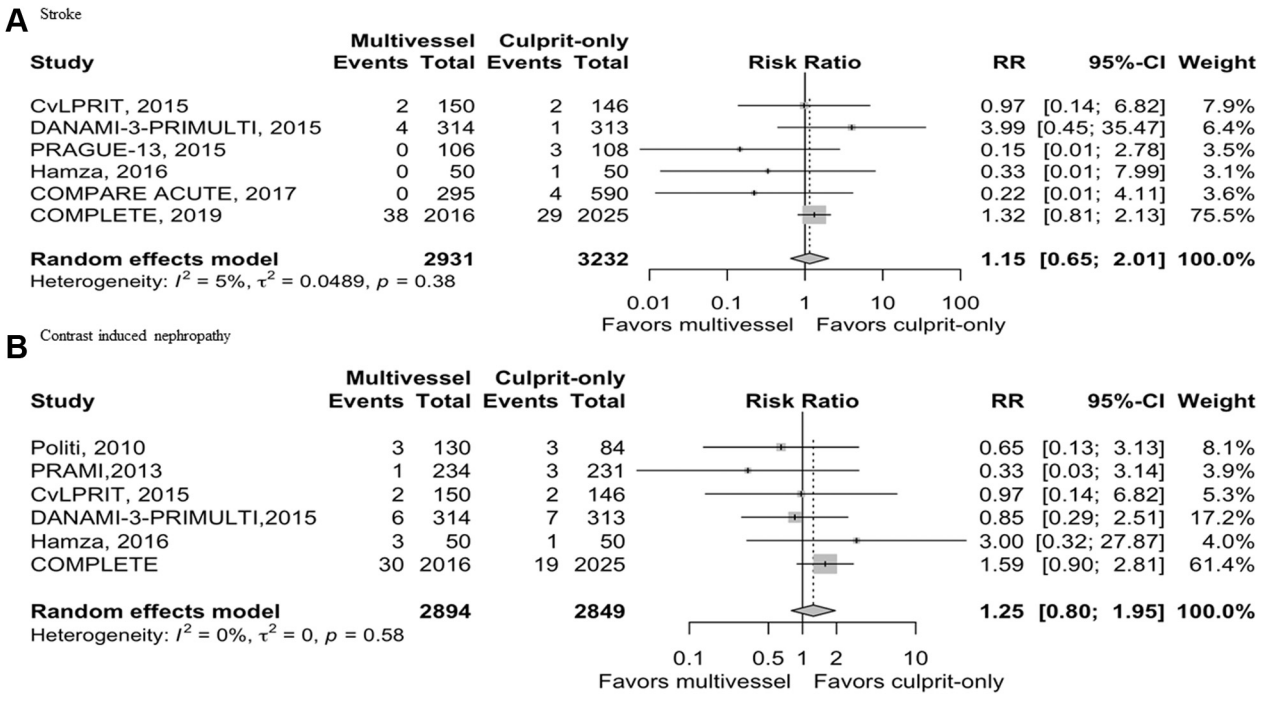
only revascularization. The magnitude of benefit of multivessel PCI in patients with STEMI is strikingly similar to that observed previously with multivessel revascularization in patients with stable CAD, suggesting that multivessel revascularization may be beneficial irrespective of the clinical syndrome at presentation in certain high-risk group of patients (7,29). Our analysis including more than 7,000 patients is more robust with the inclusion of the most recent COMPLETE trial and is designed to have sufficient power (92%) on the basis of our power analysis to detect a meaningful reduction in hard endpoints of all-cause mortality (19). Furthermore, the techniques of PCI have undergone significant advancement, with more operators able to perform primary multivessel PCI with door-to-balloon times <90 min, which also significantly contributed to overall improved clinical outcomes.

However, it is noteworthy that a small number of patients may experience periprocedural MI from repeat revascularization, which may be masked when PCI is performed in the setting of STEMI, somewhat overestimating the benefit of multivessel PCI with regard to the primary clinical outcome of reinfarction.

Similar to the prior RCTs and meta-analyses, we observed a significantly lower incidence of repeat revascularization with multivessel PCI compared with culprit vessel–only PCI. Coronary lesions in nonculprit vessels have been correlated to adverse cardiac events (30). Secondary plaque rupture in a nonculprit coronary artery is more common after acute MI than after stable angina (31). In a prospective study of the natural history of atherosclerosis in a post-acute coronary syndrome population, Stone et al. (32) reported that nearly 50% of future major adverse cardiovascular events during 3-year follow-up occurred in nonculprit bystander lesions. Interestingly, most of the nonculprit lesions responsible for future major adverse cardiovascular events were angiographically mild at baseline. So, the possibility of leaving these nonculprit lesions unstented in RCTs that used angiography for multivessel revascularization is very high. Other noninvasive techniques (computed tomographic calcium scoring, coronary computed tomographic angiography, magnetic resonance) or intravascular ultrasound markers such as thin-cap fibroatheroma and minimal luminal area, which are known to identify unstable plaques and also predict future major adverse cardiovascular events, may be considered in future studies evaluating the 2 revascularization techniques (30,33).

The timing of revascularization has been a subject of debate over the years, with data from previous studies showing contrasting results (26,34). Sensitivity analysis of 1,964 patients (5 clinical trials) including multivessel PCI during index hospitalization (Supplemental Figure 1) demonstrated a 49% relative risk reduction in cardiovascular mortality ($p = 0.03$), a 38% reduction in all-cause mortality ($p = 0.04$), and a 64% reduction in repeat revascularization ($p < 0.0001$), with a similar risk for stroke and major bleeding. Furthermore, on meta-regression, we observed that index revascularization of the nonculprit vessel significantly affected reinfarction. On the basis of these data, we suggest that the updated guidelines should take into

FIGURE 4 Secondary Safety Outcomes



Forest plots showing stroke **(A)** and contrast-induced nephropathy **(B)**.

consideration the benefits of multivessel PCI during index hospitalization in patients presenting with STEMI. Other factors that can influence decision making in patients with multivessel CAD at the time of STEMI presentation have been reported previously (35). We also demonstrate the safety of multivessel PCI, with additional interventions not leading to a measurable increase in the risk for complications such as major bleeding, stroke, or CIN compared with culprit vessel-only PCI.

Finally, our results do not apply to patients in cardiogenic shock. The CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial demonstrated increased mortality among patients who underwent multivessel PCI compared with culprit vessel-only PCI in acute MI with cardiogenic shock in both the short term and the long term (36,37). It is important to note that patients with high-risk features such as cardiogenic shock were excluded from the RCTs that were pooled in our study. Moreover, revascularization of chronic total occlusion, which was found to be nonbeneficial even in patients with STEMI without cardiogenic shock, was performed in at least a quarter of CULPRIT-SHOCK trial participants (38). Thus, differences in baseline and procedural characteristics may explain the variation in results.

STUDY LIMITATIONS. First, the sample size of included studies, except for the COMPLETE trial, was small. Therefore, the results of our meta-analysis could have been skewed toward biases within the COMPLETE trial. However, we performed a power analysis, which demonstrated that our population was adequate to estimate differences in hard clinical endpoints of all-cause mortality.

Second, a potential favorable effect of multivessel PCI compared with culprit-only PCI with regard to cardiovascular mortality must be interpreted in the light of disparities in the available data, such as missing cardiovascular mortality data in 3 clinical trials that reported only all-cause mortality (10,14,15) and wide CIs in the point estimates of the rest of the trials (other than COMPLETE) (8,9,11-13,16,19).

Third, there was variation in follow-up duration, and the included trials were conducted in different time periods. There was also variation in the timing of non-culprit vessel PCI between the studies.

Fourth, 4 trials used FFR-guided multivessel PCI, which is associated with high sensitivity and specificity for identifying ischemic lesions (39). There was variation in the FFR cutoff criteria for stenting the nonculprit vessel.

Fifth, trial participants are highly selected patients, so generalizing such results to sicker patients in daily clinical practice should be undertaken with caution.

Sixth, our results do not apply for late STEMI presentations, as there is no consensus regarding optimal timing and PCI strategy in those patients.

Seventh, patients presenting with STEMI and revascularization were not included in the trials, so unfortunately we are not able to comment on the treatment of performing multivessel complete revascularization in this group of patients. However, it is not our general practice to target noncluprit chronic total occlusion in the setting of STEMI.

Finally, publication bias is an inherent limitation of any meta-analysis.

CONCLUSIONS

In patients with STEMI with multivessel CAD, multivessel PCI compared with culprit vessel–only PCI was associated with lower risk for reinfarction, with no difference in all-cause mortality.

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PERSPECTIVES

WHAT IS KNOWN? Nearly half of patients presenting with STEMI have at least 1 obstructive lesion in a nonculprit vessel at the time of index PCI. There is discordance of American and European guidelines regarding revascularization of these nonculprit lesions.

WHAT IS NEW? The present study shows that multivessel revascularization was associated with lower risk for reinfarction, without any difference in all-cause mortality.

WHAT IS NEXT? Future research should evaluate the optimal timing of non–culprit vessel revascularization in patients with STEMI.

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KEY WORDS cardiovascular mortality, contrast-induced nephropathy, culprit vessel–only revascularization, major adverse cardiac events, multivessel coronary artery disease, multivessel revascularization, reinfarction, repeat revascularization, ST-segment elevation myocardial infarction

APPENDIX For supplemental tables and figures, please see the online version of this paper.