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Complete vs Culprit-Lesion-Only Revascularization for ST-Segment Elevation Myocardial Infarction
A Systematic Review and Meta-analysis

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IMPORTANCE Recently, the Complete vs Culprit-Only Revascularization to Treat Multivessel Disease After Early PCI (percutaneous coronary intervention) for STEMI (ST-segment elevation myocardial infarction [MI]) (COMPLETE) trial showed that angiography-guided PCI of the nonculprit lesion with the goal of complete revascularization reduced cardiovascular (CV) death or new MI compared with PCI of the culprit lesion only in STEMI. Whether complete revascularization also reduces CV mortality is uncertain. Moreover, whether the association of complete revascularization with hard clinical outcomes is consistent when fractional flow reserve (FFR)– and angiography-guided strategies are used is unknown.

OBJECTIVE To determine through a systematic review and meta-analysis (1) whether complete revascularization is associated with decreased CV mortality and (2) whether heterogeneity in the association occurs when FFR- and angiography-guided PCI strategies for nonculprit lesions are performed.

DATA SOURCES A systematic search of MEDLINE, Embase, ISI Web of Science, and CENTRAL (Cochrane Central Register of Controlled Trials) from database inception to September 30, 2019, was performed. Conference proceedings were also reviewed from January 1, 2002, to September 30, 2019.

STUDY SELECTION English-language randomized clinical trials comparing complete revascularization vs culprit-lesion-only PCI in patients with STEMI and multivessel disease were included.

DATA EXTRACTION AND SYNTHESIS The combined odds ratio (OR) was calculated with the random-effects model using the Mantel-Haenszel method (sensitivity with fixed-effects model). Heterogeneity was measured using the I^2 statistic. Publication bias was evaluated using the inverted funnel plot approach. Data were analyzed from October 2019 to January 2020.

MAIN OUTCOMES AND MEASURES Cardiovascular death and the composite of CV death or new MI.

RESULTS Ten randomized clinical trials involving 7030 unique patients were included. The weighted mean follow-up time was 29.5 months. Complete revascularization was associated with reduced CV death compared with culprit-lesion-only PCI (80 of 3191 [2.5%] vs 106 of 3406 [3.1%]; OR, 0.69 [95% CI, 0.48-0.99]; $P = .05$; fixed-effects model OR, 0.74 [95% CI, 0.55-0.99]; $P = .04$). All-cause mortality occurred in 153 of 3426 patients (4.5%) in the complete revascularization group vs 177 of 3604 (4.9%) in the culprit-lesion-only group (OR, 0.84 [95% CI, 0.67-1.05]; $P = .13$; $I^2 = 0\%$). Complete revascularization was associated with a reduced composite of CV death or new MI (192 of 2616 [7.3%] vs 266 of 2586 [10.3%]; OR, 0.69 [95% CI, 0.55-0.87]; $P = .001$; fixed-effects model OR, 0.69 [95% CI, 0.57-0.84]; $P < .001$), with no heterogeneity in this outcome when complete revascularization was performed using an FFR-guided strategy (OR, 0.78 [95% CI, 0.43-1.44]) or an angiography-guided strategy (OR, 0.61 [95% CI, 0.38-0.97]; $P = .52$ for interaction).

CONCLUSIONS AND RELEVANCE In patients with STEMI and multivessel disease, complete revascularization was associated with a reduction in CV mortality compared with culprit-lesion-only PCI. There was no differential association with treatment between FFR- and angiography-guided strategies on major CV outcomes.

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Supplemental content

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The 2017 European Society of Cardiology guidelines for management of ST-segment elevation myocardial infarction (STEMI) state that routine revascularization of non-infarct-related artery lesions should be considered in patients with multivessel disease before hospital discharge with a class IIA (level of evidence A) recommendation.[1] The 2015 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions focused update on STEMI supports nonculprit-vessel intervention as a class IIB (level of evidence B) recommendation.[2] These recommendations were based on the results of recent randomized clinical trials (RCTs) and meta-analyses documenting improved outcomes with complete revascularization with percutaneous coronary intervention (PCI) in STEMI. However, these results have been driven mainly by composite end points that include subsequent ischemia-driven revascularization.[3] Recently, the Complete vs Culprit-Only Revascularization to Treat Multivessel Disease After Early PCI for STEMI (COMPLETE) study demonstrated that a strategy of complete revascularization with staged PCI of the nonculprit lesion reduced the composite of cardiovascular (CV) death and new myocardial infarction (MI).[4] The COMPLETE trial was not powered to detect reductions in CV death alone, hence it remains uncertain whether complete revascularization reduces this outcome. In addition, it is unclear whether a difference in CV events occurs when a fractional flow reserve (FFR)- or an angiography-guided strategy is used for complete revascularization. Accordingly, we performed a collaborative meta-analysis of RCTs to determine (1) whether complete revascularization is associated with decreased CV mortality and (2) the consistency of the association when FFR- and angiography-guided nonculprit-lesion PCI strategies are performed.

Key Points

Question Compared with a culprit-lesion-only percutaneous coronary intervention strategy, is a strategy of complete revascularization with multivessel percutaneous coronary intervention associated with decreased cardiovascular mortality in ST-segment elevation myocardial infarction, and what is the association when fractional flow reserve– and angiography-guided complete revascularization approaches are used?

Findings In this systematic review and meta-analysis of 10 randomized clinical trials of 7030 unique patients, a 31% relative risk reduction in cardiovascular death (no significant reduction in all-cause mortality) was associated with a complete revascularization strategy. Consistent associations were found when a fractional flow reserve– or angiography-guided complete revascularization approach was used.

Meaning These results potentially extend the benefit of a complete revascularization strategy to include a reduction in cardiovascular mortality with a consistent benefit of a fractional flow reserve– or angiography-guided percutaneous coronary intervention approach on hard clinical events.

Methods

The present systematic review and meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Reviews and Interventions.[5] Analysis is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement in health care interventions.

Search Strategy

We searched PubMed/MEDLINE, Ovid/Embase, ISI Web of Science, and CENTRAL (Cochrane Central Register of Controlled Trials) from database inception through the final search date of September 30, 2019, for studies published in English. Conference presentations and abstracts from the American Heart Association, American College of Cardiology, Transcatheter Therapeutics, European Society of Cardiology, and EuroPCR were hand-searched from January 1, 2002, to September 30, 2019. Reference lists of included studies, relevant articles, and related systematic reviews were assessed. The search strategy used the following keywords: "ST elevation myocardial infarction," "myocardial infarction," "complete revascularization," "multivessel revascularization," and "nonculprit coronary artery" (eTable in the Supplement).

Study Selection

Two reviewers (K.R.B., S.R.M.) independently screened for RCTs comparing complete vs culprit-lesion-only PCI in patients with STEMI and multivessel disease. Only RCTs comparing multivessel vs culprit-lesion-only PCI in patients with STEMI and multivessel disease undergoing primary PCI were included. Studies enrolling patients with a diagnosis other than STEMI or comparing revascularization strategies other than PCI were excluded. Full-text citations and abstracts (ie, unpublished) were selected and independently screened for eligibility. Unpublished citations were intentionally included to mitigate publication bias. A PRISMA flow diagram can be found in eFigure 1 in the Supplement.

Data Abstraction

Information regarding the study design, intervention performed, number of patients enrolled, inclusion and exclusion criteria, clinical outcomes, and follow-up duration was obtained. The quality of abstracted studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias for randomized studies. Only results calculated using the intention-to-treat principle were included.

Outcomes

Information regarding CV death and a composite of CV death or new MI were collected. The composite outcome was stratified according to FFR- or angiography-guided PCI.

Statistical Analysis

Data were analyzed from October 2019 to January 2020. All statistical analysis was performed using Review Manager, version 5 (Cochrane Center). Odds ratios (ORs) with 95% CIs were used as summary estimates. The pooled OR was calculated with

the random-effects model using the Mantel-Haenszel method. Heterogeneity was measured using the I^2 statistic ([I^2 – Q – df]/Q], where Q is the χ^2 statistic and df is degrees of freedom). A value for I^2 of 0 to 30% represents low heterogeneity; greater than 30% to 60%, moderate heterogeneity; and greater than 60% to 90%, severe heterogeneity (ie, should be explored). Values greater than 90% to 100% must be evaluated with extreme caution. The potential for publication bias was evaluated using the inverted funnel plot approach. Two-sided $P < .05$ indicated significance and was calculated using a z test of the null hypothesis that there is no average effect in the random-effects model of complete revascularization versus culprit-lesion-only PCI.

Sensitivity Analysis

A pooled OR with 95% CI was calculated for the outcomes using a fixed-effects model with the Mantel-Haenszel method. A pooled OR with 95% CI was calculated for CV mortality with the addition of the CULPRIT-SHOCK (Culprit Lesion Only PCI Vs Multivessel PCI in Cardiogenic Shock) trial.[6]

Results

Search and Selection of Studies

In total, 125 abstracts were identified, and 31 were selected for full-text or abstract (unpublished) review. Of these 31 eligible studies, 21 were excluded for the following reasons: therapies were not randomly allocated (n = 14), a control group was not identified (n = 3), patients without STEMI were included (n = 3), or coronary artery bypass grafting surgery was performed (n = 1). Ten RCTs fulfilled the eligibility criteria and were included in the present systematic review.[4,7-15] The inverted funnel plots for the primary outcome of CV mortality alone and CV mortality or new MI did not suggest publication bias (eFigures 2 and 3 in the Supplement).

Included Studies

Ten RCTs of complete vs culprit-lesion-only PCI involving 7030 patients (3426 undergoing complete revascularization and 3604 undergoing culprit-lesion-only PCI) were included.[4,7-15] The weighted mean follow-up time was 29.5 months. The **Table** presents the characteristics of the included studies. Three studies performed complete revascularization with FFR-guided nonculprit-lesion PCI,[9,12,15] whereas the 7 remaining studies used an angiography-guided approach for nonculprit-lesion PCI.[4,7,8,10,11,13,14] Complete revascularization with multivessel PCI was performed exclusively during the same sitting in 2 studies[7,10] and largely during the same sitting in a further 2 studies.[13,15] In 1 study,[8] nonculprit-lesion PCI was performed during the same sitting or as a staged procedure. In the 4 remaining studies,[4,9,11,12] complete revascularization was performed only as a staged procedure.

Clinical Outcomes

Cardiovascular Death

A total of 80 CV deaths (2.5%) occurred in 3191 patients undergoing complete revascularization compared with 106 (3.1%) in 3406 patients undergoing culprit-lesion-only PCI, a 31% relative risk reduction, among the 7 trials reporting this outcome[4,7,8,10,12,13,15] (OR, 0.69 [95% CI, 0.48-0.99]; $P = .05$; $I^2 = 9\%$) (**Figure 1**). Similar results were observed using a fixed-effects model (OR, 0.74 [95% CI, 0.55-0.99]; $P = .04$; $I^2 = 9\%$).

Among the 10 studies reporting all-cause death,[4,7-15] 153 deaths (4.5%) among 3426 patients occurred with complete revascularization vs 177 deaths (4.9%) among 3604 patients with culprit-lesion-only PCI (OR, 0.84 [95% CI, 0.67-1.05]; $P = .13$; $I^2 = 0\%$) (eFigure 4 in the Supplement). Similar results were observed using a fixed-effects model (OR, 0.84 [95% CI, 0.67-1.05]; $P = .13$; $I^2 = 0\%$).

CV Death or New MI

Four studies[4,7,10,12] reported CV death or new MI (**Figure 2**). Among these studies, 192 events (7.3%) occurred in the 2616 patients undergoing complete revascularization compared with 266 events (10.3%) in 2586 patients undergoing the culprit-lesion-only strategy (OR, 0.69 [95% CI, 0.55-0.87]; $P = .001$; $I^2 = 6\%$). Similar results were noted using a fixed-effects model (OR, 0.69 [95% CI, 0.57-0.84]; $P < .001$; $I^2 = 6\%$).

New MI

Ten studies[4,7-15] reported new MI (eFigure 5 in the Supplement). A total of 175 new MIs (5.1%) occurred in the 3426 patients undergoing complete revascularization compared with 247 (6.9%) in 3604 patients undergoing culprit-lesion-only PCI (OR, 0.68 [95% CI, 0.49-0.96]; $P = .03$; $I^2 = 26\%$). This result was consistent when a fixed-effects model was used (OR, 0.70 [95% CI, 0.57-0.85]; $P < .001$; $I^2 = 26\%$).

FFR- vs Angiography-Guided Nonculprit-Lesion PCI

For CV death or new MI, a consistent benefit with complete revascularization was found compared with culprit-lesion-only PCI when an FFR-guided nonculprit-lesion PCI strategy was used (OR, 0.78 [95% CI, 0.43-1.44]; $P = .43$) and when an angiography-guided nonculprit-lesion PCI strategy was used (OR, 0.61 [95% CI, 0.38-0.97]; $P = .04$; $I^2 = 34\%$), with no evidence of heterogeneity between these subgroups ($P = .52$ for interaction) (**Figure 3**). Similarly, no differential association of treatment was found between an FFR-guided (OR, 0.69 [95% CI, 0.29-1.64]; $P = .40$; $I^2 = 0\%$) or an angiography-guided (OR, 0.57 [95% CI, 0.32-1.03]; $P = .06$; $I^2 = 34\%$) complete revascularization strategy compared with a culprit-lesion-only strategy on CV death alone ($P = .73$ for interaction) (**Figure 4**). In addition, there was no differential association with treatment between FFR-guided multivessel PCI (OR, 1.03 [95% CI, 0.32-3.29]; $P = .95$; $I^2 = 70\%$) or angiography-guided multivessel PCI (OR, 0.65 [95% CI, 0.52-0.82]; $P < .001$; $I^2 = 0\%$) on MI alone ($P = .44$ for interaction) (eFigure 6 in the Supplement).

Single-Sitting vs Staged Approach to Complete Revascularization

In an analysis stratified by timing of nonculprit-lesion PCI, complete revascularization compared with culprit-lesion-only PCI was associated with reduced CV death or new MI in patients undergoing same-sitting multivessel PCI (OR, 0.41 [95% CI, 0.20-0.81]; $P = .01$; $I^2 = 0\%$) as well those treated with a staged

Table. Summary of 10 RCTs Comparing Complete Revascularization With Culprit-Lesion-Only PCI

Source	Intervention	No. of patients	Inclusion criteria	Exclusion criteria	Primary outcome
Di Mario et al,[7] 2004	Culprit-vessel PCI with additional revascularization at the investigators' discretion vs culprit-vessel PCI with immediate multivessel treatment during index catheterization	69	STEMI with MVD and 1-3 lesions in nonculprit artery technically amenable to revascularization by stent	Lesion in vein and arterial grafts, prior angioplasty, thrombolysis, cardiogenic shock, LM disease	12-mo Incidence of repeated revascularization (any revascularization, IRA as well as non-IRA)
Politi et al,[8] 2010	Culprit-vessel PCI vs culprit-vessel PCI plus multivessel PCI during index catheterization or staged procedure	214	STEMI with >70% stenosis of ≥2 coronary arteries or major branches	Cardiogenic shock, LM disease, previous CABG, severe valvular heart disease, unsuccessful procedure	Mean: 30-mo MACE defined as cardiac or noncardiac death, in-hospital death, reinfarction, rehospitalization for acute coronary syndrome, repeated coronary revascularization
Ghani et al,[9] 2012	Culprit-vessel PCI with ischemia-guided additional revascularization only if symptoms recurred vs culprit-vessel PCI plus PCI of severe lesion (>90%) or FFR-guided PCI in vessels with significant stenosis (<90%) as a staged procedure	119	STEMI with >50% stenosis of ≥2 epicardial arteries	Urgent revascularization, aged >80 y, CTO of non-IRA, prior CABG, LM≥50%, ISR in non-IRA, chronic atrial fibrillation, limited life expectancy, other factors that make follow-up unlikely	36-mo MACE defined as death, nonfatal reinfarction, additional revascularization procedures
Wald et al,[10] 2013	Culprit-vessel-only PCI vs preventive PCI with culprit- and nonculprit-vessel PCI performed during the index catheterization	465	STEMI with MVD of >50% stenosis of ≥2 epicardial arteries	Cardiogenic shock, LM disease, previous CABG, CTO	Mean: 23-mo death due to cardiac causes, nonfatal MI, refractory angina
Gershlick et al,[13] 2015	Culprit-only PCI vs complete revascularization mainly index admission (mainly same sitting)	296	STEMI of <12 h onset with MVD and noninfarct artery stenosis >70%	Cardiogenic shock, prior CABG, CKD, VSD, severe MR, previous q wave infarction	12-mo All-cause death, recurrent MI, heart failure, ischemia-driven revascularization
Engstrøm et al,[12] 2015	Culprit-only PCI vs complete FFR-guided revascularization as a staged PCI (2 d later)	627	STEMI of <12 h onset with MVD and noninfarct artery stenosis >70%	Cardiogenic shock, stent thrombosis, CABG, intolerance of contrast media, increased bleeding risk	Median (range): 27 (12-44)-mo all-cause mortality, nonfatal MI, ischemia-driven revascularization of lesions in non-IRAs
Hlinomaz et al,[11] 2015	Culprit-only PCI vs complete revascularization as a staged PCI (3-40 d later)	214	STEMI with MVD and noninfarct artery stenosis ≥70%	Cardiogenic shock, LM disease, significant valve disease, angina (CCS II) lasting 1 mo before STEMI	Median: 38-mo all-cause mortality, nonfatal MI, stroke
Hamza et al,[14] 2016	Culprit-vessel-only vs complete revascularization during index procedure or staged within 72 h in patients with diabetes	100	STEMI with MVD in patients with diabetes within 12 h of symptoms	MVD with 50%-70% stenosis, CTO, prior CABG, LM disease	6-mo All-cause mortality, recurrent MI, ischemia-driven revascularization
Smits et al,[15] 2017	Culprit-vessel-only vs FFR-guided multivessel PCI during the index procedure	885	STEMI with MVD that was appropriate for FFR and PCI	Hemodynamically unstable	12-mo Death due to any cause, nonfatal MI, revascularization, cerebrovascular event
Mehta et al,[4] 2019	Culprit-vessel-only vs staged complete revascularization either in hospital or electively (within 45 d)	4041	STEMI randomized within 72 h after culprit-lesion PCI	Prerandomization revascularization of a nonculprit lesion, planned surgical intervention, prior CABG	3-y Coprimary outcome of a composite of cardiovascular death or new MI and composite of cardiovascular death, new MI, or ischemia-driven revascularization

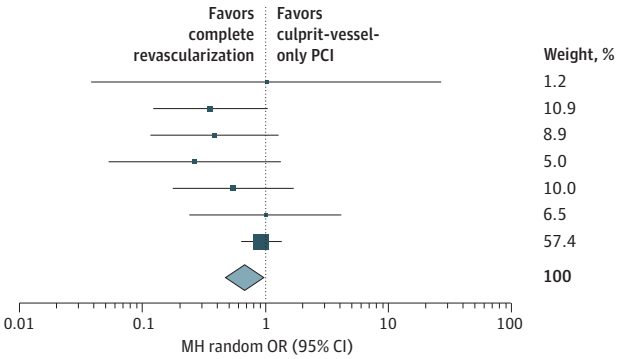
Abbreviations: CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CTO, chronic total occlusion; FFR, fractional flow reserve; IRA, infarct-related artery; ISR, in-stent restenosis; LM, left main; MACE, major adverse cardiovascular events; MI, myocardial infarction; MR, mitral regurgitation; MVD, multivessel disease; PCI, percutaneous coronary intervention; RCT, randomized clinical trial; STEMI, ST-segment elevation myocardial infarction; VSD, ventricular septal defect.

approach (OR, 0.73 [95% CI, 0.60-0.89]; P = .002; I^2 = 0%), with no difference in the association of treatment (P = .11 for interaction) (eFigure 7 in the Supplement). Similar findings were observed with the individual end points of CV death alone for same-sitting PCI (OR, 0.49 [95% CI, 0.26-0.94]; P = .03; I^2 = 0%) and staged-approach PCI (OR, 0.88 [95% CI, 0.62-1.24]; P = .46; I^2 = 0%; P = .12 for interaction) (eFigure 8 in the Supplement) and MI alone for same-sitting PCI (OR, 0.46

Figure 1. Forest Plot of Long-term Cardiovascular Death in Patients With Complete Revascularization or Culprit-Lesion-Only Percutaneous Coronary Intervention (PCI)

Source or study	Complete revascularization No. of events	Complete revascularization Total No.	Culprit-vessel-only PCI No. of events	Culprit-vessel-only PCI Total No.	MH random OR (95% CI)	Weight, %
HELP AMI,[7] 2004	1	52	0	17	1.02 (0.04-26.19)	1.2
Politi et al,[8] 2010	6	130	10	84	0.36 (0.13-1.03)	10.9
PRAMI,[10] 2013	4	234	10	231	0.38 (0.12-1.24)	8.9
CvLPRIT,[13] 2015	2	150	7	146	0.27 (0.05-1.31)	5.0
DANAMI-3-PRIMULTI,[12] 2015	5	314	9	313	0.55 (0.18-1.65)	10.0
COMPARE-ACUTE,[15] 2017	3	295	6	590	1.00 (0.25-4.03)	6.5
COMPLETE,[4] 2019	59	2016	64	2025	0.92 (0.64-1.32)	57.4
Total	**80**	**3191**	**106**	**3406**	**0.69 (0.48-0.99)**	**100**

Heterogeneity: $\tau = 0.03$; $\chi^2_8 = 6.57$ ($P = .36$); $I^2 = 9\%$
Test for overall effect: $z = 1.99$ ($P = .05$)

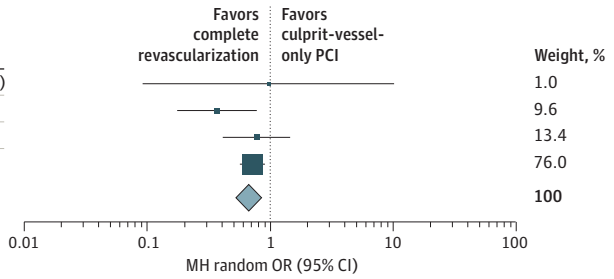


Size of markers represents weight. Squares and diamonds indicate odds ratios (ORs); error bars, 95% CIs. COMPARE-ACUTE indicates Fractional Flow Reserve Guided Primary Multivessel Percutaneous Coronary Intervention to Improve Guideline Indexed Actual Standard of Care for Treatment of ST-Elevation Myocardial Infarction in Patients With Multivessel Coronary Disease; COMPLETE, Complete vs Culprit-Only Revascularization to Treat Multivessel Disease After Early PCI for STEMI; CvLPRIT, Complete vs Lesion-Only Primary PCI Trial; DANAMI-3–PRIMULTI, 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; MH random, random-effects model using the Mantel-Haenszel method; and PRAMI, Preventive Angioplasty in Myocardial Infarction.

Figure 2. Forest Plot of Long-term Cardiovascular Death or New Myocardial Infarction in Patients With Complete Revascularization or Culprit-Lesion-Only Percutaneous Coronary Intervention (PCI)

Source or study	Complete revascularization No. of events	Complete revascularization Total No.	Culprit-vessel-only PCI No. of events	Culprit-vessel-only PCI Total No.	MH random OR (95% CI)	Weight, %
HELP AMI,[7] 2004	3	52	1	17	0.98 (0.10-10.09)	1.0
PRAMI,[10] 2013	11	234	27	231	0.37 (0.18-0.77)	9.6
DANAMI-3-PRIMULTI,[12] 2015	20	314	25	313	0.78 (0.43-1.44)	13.4
COMPLETE,[4] 2019	158	2016	213	2025	0.72 (0.58-0.90)	76.0
Total	**192**	**2616**	**266**	**2586**	**0.69 (0.55-0.87)**	**100**

Heterogeneity: $\tau = 0.01$; $\chi^2_3 = 3.19$ ($P = .36$); $I^2 = 6\%$
Test for overall effect: $z = 3.18$ ($P = .001$)



Size of markers represents weight. Squares and diamonds indicate odds ratios (ORs); error bars, 95% CIs. COMPLETE indicates Complete vs Culprit-Only Revascularization to Treat Multivessel Disease After Early PCI for STEMI; DANAMI-3–PRIMULTI, 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; MH random, random-effects model using the Mantel-Haenszel method; and PRAMI, Preventive Angioplasty in Myocardial Infarction.

[95% CI, 0.27-0.77]; $P = .003$; $I^2 = 0\%$) and staged PCI (OR, 0.93 [95% CI, 0.55-1.58]; $P = .80$; $I^2 = 50\%$; $P = .06$ for interaction) (eFigure 9 in the Supplement).

As a sensitivity analysis, we added the results of CV mortality (sudden cardiac death, death due to cardiogenic shock, or death due to recurrent MI) from the CULPRIT-SHOCK trial.[6] We found a directionally consistent result for CV mortality (OR, 0.80 [95% CI, 0.58-1.09]; $P = .15$; $I^2 = 25\%$) (eFigure 10 in the Supplement).

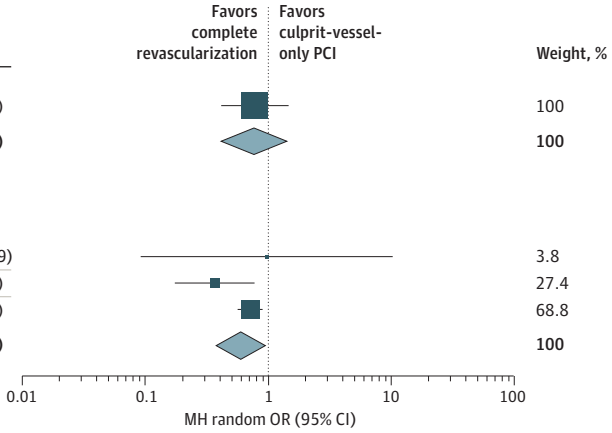
Discussion

In the largest meta-analysis performed to date, a strategy of complete revascularization with nonculprit-lesion PCI was associated with a reduction in CV mortality compared with a strategy of culprit-lesion-only PCI in patients with STEMI and multivessel disease without cardiogenic shock at presentation. Furthermore, we have shown a reduction in the composite outcome of CV death or new MI with complete revascularization irrespective of whether it is performed with an FFR- or an angiography-guided nonculprit-lesion PCI strategy.

None of the individual RCTs comparing complete revascularization with a culprit-lesion-only strategy were adequately powered to detect reductions in CV mortality. In the largest meta-analysis, to our knowledge, involving more than 7000 patients from these trials, we observed a 31% relative risk reduction in CV mortality with complete revascularization. Although this outcome was nominally significant, a fixed-effects analysis demonstrated a similar outcome. Moreover, our findings have been confirmed in a recent meta-analysis of 6 randomized studies[16] (6528 patients) showing a 38% reduction in CV death. This reduction in CV mortality is consistent with a robust reduction in new MI observed with complete re-

Figure 3. Forest Plot of Long-term Cardiovascular Death or New Myocardial Infarction Stratified by Approach in Patients With Complete Revascularization or Culprit-Lesion-Only Percutaneous Coronary Intervention (PCI)

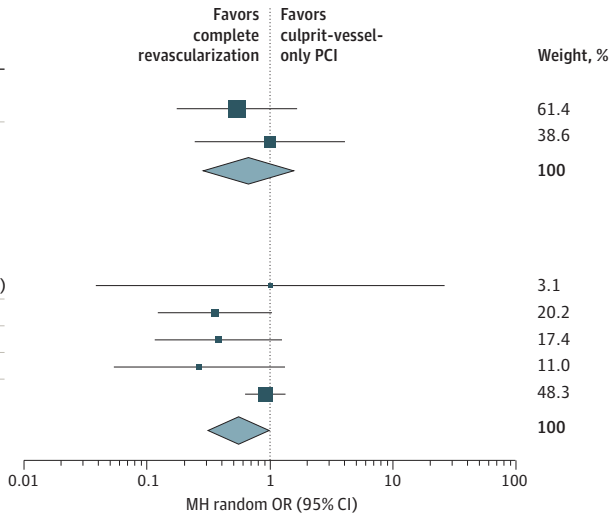
Source or study	Complete revascularization No. of events	Complete revascularization Total No.	Culprit-vessel-only PCI No. of events	Culprit-vessel-only PCI Total No.	MH random OR (95% CI)	Weight, %
FFR-guided nonculprit lesion PCI						
DANAMI-3-PRIMULTI,[12] 2015	20	314	25	313	0.78 (0.43-1.44)	100
Total	**20**	**314**	**25**	**313**	**0.78 (0.43-1.44)**	**100**
Heterogeneity: not applicable Test for overall effect: $z = 0.78$ ($P = .43$)						
Angiography-guided nonculprit lesion PCI						
HELP AMI,[7] 2004	3	52	1	17	0.98 (0.10-10.09)	3.8
PRAMI,[10] 2013	11	234	27	231	0.37 (0.18-0.77)	27.4
COMPLETE,[4] 2019	158	2016	213	2025	0.72 (0.58-0.90)	68.8
Total	**172**	**2302**	**241**	**2273**	**0.61 (0.38-0.97)**	**100**
Heterogeneity: $\tau = 0.07$; $\chi^2_2 = 3.03$ ($P = .22$); $I^2 = 34\%$ Test for overall effect: $z = 2.07$ ($P = .04$)						
Test for subgroup differences: $\chi^2_1 = 0.41$ ($P = .52$); $I^2 = 0\%$						



Patients were stratified by a fractional flow reserve (FRR)– vs angiography-guided nonculprit-lesion approach. Size of markers represents weight. Squares and diamonds indicate odds ratios (ORs); error bars, 95% CIs. COMPLETE, Complete vs Culprit-Only Revascularization to Treat Multivessel Disease After Early PCI for STEMI; DANAMI-3–PRIMULTI, 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; MH random, random-effects model using the Mantel-Haenszel method; and PRAMI, Preventive Angioplasty in Myocardial Infarction.

Figure 4. Forest Plot of Long-term Cardiovascular Death Stratified by Approach in Patients With Complete Revascularization or Culprit-Lesion-Only Percutaneous Coronary Intervention (PCI)

Source or study	Complete revascularization No. of events	Complete revascularization Total No.	Culprit-vessel-only PCI No. of events	Culprit-vessel-only PCI Total No.	MH random OR (95% CI)	Weight, %
FFR-guided nonculprit lesion PCI						
DANAMI-3-PRIMULTI,[12] 2015	5	314	9	313	0.55 (0.18-1.65)	61.4
COMPARE-ACUTE,[15] 2017	3	295	6	590	1.00 (0.25-4.03)	38.6
Total	**8**	**609**	**15**	**903**	**0.69 (0.29-1.64)**	**100**
Heterogeneity: $\tau = 0.00$; $\chi^2_1 = 0.44$ ($P = .51$); $I^2 = 0\%$ Test for overall effect: $z = 0.84$ ($P = .40$)						
Angiography-guided nonculprit lesion PCI						
HELP AMI,[7] 2004	1	52	0	17	1.02 (0.04-26.19)	3.1
Politi et al,[8] 2010	6	130	10	84	0.36 (0.13-1.03)	20.2
PRAMI,[10] 2013	4	234	10	231	0.38 (0.12-1.24)	17.4
CvLPRIT,[13] 2015	2	150	7	146	0.27 (0.05-1.31)	11.0
COMPLETE,[4] 2019	59	2016	64	2025	0.92 (0.64-1.32)	48.3
Total	**72**	**2582**	**91**	**2503**	**0.57 (0.32-1.03)**	**100**
Heterogeneity: $\tau = 0.15$; $\chi^2_4 = 6.09$ ($P = .19$); $I^2 = 34\%$ Test for overall effect: $z = 1.87$ ($P = .06$)						
Test for subgroup differences: $\chi^2_1 = 0.12$ ($P = .73$); $I^2 = 0\%$						



Patients were stratified by a fractional flow reserve (FRR)– vs angiography-guided nonculprit-lesion approach. Size of markers represents weight. Squares and diamonds indicate odds ratios (ORs); error bars, 95% CIs. COMPLETE indicates Complete vs Culprit-Only Revascularization to Treat Multivessel Disease After Early PCI for STEMI; CvLPRIT, Complete vs Lesion-Only Primary PCI Trial; DANAMI-3–PRIMULTI, 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; MH random, random-effects model using the Mantel-Haenszel method; and PRAMI, Preventive Angioplasty in Myocardial Infarction.

vascularization. Results from the Optical Coherence Tomography (OCT) COMPLETE substudy have demonstrated that approximately one-half of obstructive nonculprit lesions contain unstable plaque morphology.[17] Hence, routine nonculprit-lesion PCI as a preventive strategy could reduce subsequent MI and potentially improve CV long-term survival.

A novel finding of our meta-analysis is the consistent benefit of an FFR- and angiography-guided, nonculprit-lesion complete revascularization approach. Although FFR might underestimate in some cases the severity of nonculprit lesions in the acute and subacute phases,[18,19] the outcomes of the FFR-guided trials were consistent with those of the angiography-

guided studies, even after deferring PCI of nonculprit lesions in 31% to 44% of the patients.[12,15] Still, a recent study has speculated regarding the accuracy of hyperemic and resting indices of nonculprit STEMI lesions,[20] and the optimal timing of performing these measurements is unclear.[21] Moreover, unlike an angiography-guided approach, the individual FFR-guided PCI trials have not shown a reduction in CV death or MI. However, a recent patient-level pooled analysis of FAME II (Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment Vs Optimal Medical Treatment Alone in Patients With Stable Coronary Artery Disease), DANAMI-PRIMULTI (Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization), and COMPARE-ACUTE (Fractional Flow Reserve Guided Primary Multivessel Percutaneous Coronary Intervention to Improve Guideline Indexed Actual Standard of Care for Treatment of ST-Elevation Myocardial Infarction in Patients With Multivessel Coronary Disease) did show a reduction in CV death or MI (mainly driven by a decreased risk of MI) with FFR-guided PCI.[22] Hence, we believe there is equipoise as to the optimal strategy for complete revascularization in STEMI with multivessel disease that needs to be addressed in a large RCT.

We demonstrated consistent benefits of complete revascularization regardless of whether the nonculprit-lesion PCI procedure was performed during the same sitting or as a staged procedure. In the COMPLETE trial, recurrent events were reduced mainly during the long term with complete revascularization, with little difference in the first 45 days after the index STEMI.[4] No heterogeneity in the association with treatment was detected in those patients with staged complete revascularization early during the index hospitalization or electively as an outpatient (≤45 days).[23] This finding suggests that early events after STEMI are mainly owing to the size and severity of the index STEMI itself rather than nonculprit lesions. Analogous to revascularization outcomes with coronary artery bypass grafting surgery, the benefits of complete revascularization with PCI appear to accrue long term. Hence, our data provide reassurance to clinicians who are contemplating the timing of complete revascularization with PCI.

In the context of our meta-analysis, the findings of the CULPRIT-SHOCK trial deserve attention. In patients with acute MI (STEMI or non-STEMI) and cardiogenic shock, a significant reduction in the primary composite of all-cause death or severe renal failure requiring renal replacement therapy was observed with a culprit-lesion-only strategy compared with compete revascularization during the index event, with an 8.2% absolute reduction in mortality at 30 days (recognizing staged revascularization was encouraged in the culprit-lesion-only strategy because 21.5% underwent staged or urgent repeated revascularization).[6] At 1 year, no significant difference in all-cause mortality was observed.[24] Although provocative, the issue with cardiogenic shock is that early mortality is high and the ability to perform complete revascularization is low (<50% in CULPRIT-SHOCK), which does not allow for proper evaluation of complete revascularization. As well, not all patients in the trial presented with STEMI (approximately 40% had non-STEMI). The studies included in our meta-analysis largely excluded cardiogenic shock.

Before the COMPLETE trial, guideline recommendations were limited to small-sample-size RCTs with lower power to detect differences in CV death or new MI. In addition, most trials included revascularization in the primary composite outcome, which is subject to criticism in an open-label trial. We now believe reasonable conclusions can be made with the results of our meta-analysis on hard clinical end points, including the potential for reduction in CV death alone. Moreover, these results appear consistent with FFR- and angiography-guided complete revascularization.

Limitations

Publication bias supporting multivessel PCI in STEMI is a potential limitation, although we included unpublished abstracts to minimize such bias. Furthermore, we performed an inverted funnel plot for CV death alone and CV death or new MI and found no publication bias (eFigures 2 and 3 in the Supplement). Individual patient data were not available for all included studies, precluding subgroup and other exploratory analyses. Admission and follow-up medications were not summarized. Follow-up left ventricular systolic function was not captured. We were not able to evaluate chronic total occlusions because most of the selected studies did not report this finding in STEMI. Limited randomized studies were available for FFR-guided multivessel PCI compared with angiographic-guided multivessel PCI, making it difficult to draw any firm conclusions on which of these approaches to complete revascularization is optimal. Finally, although we did find a significant reduction in CV mortality, the largest trial, COMPLETE, did not show a significant reduction in CV mortality alone but was not powered for this outcome (hence the reason for performing this meta-analysis). Still, we acknowledge the contribution of smaller RCTs with large CV mortality differences, which could conceivably influence our results.

Conclusions

Among patients with STEMI and multivessel disease, our meta-analysis involving 7030 patients found complete revascularization was associated with reduction in CV death compared with a culprit-lesion-only PCI in patients without cardiogenic shock at presentation. Moreover, consistency in the results was found for hard clinical outcomes when an FFR- or angiography-guided nonculprit-lesion PCI approach was used.

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