

FFR- Versus Angiography-Guided Revascularization for Nonculprit Stenosis in STEMI and Multivessel Disease



A Network Meta-Analysis

Ayman Elbadawi, MD,^{a,*} Alexander T. Dang, MD,^{b,*} Mohamed Hamed, MD,^c Mennaallah Eid, MD,^d Meghana Prakash Hiriyur Prakash, MD,^e Mohammed Saleh, MD,^f Mohamed Gad, MD,^g Mamas A. Mamas, MD, PhD,^{h,i} Faisal Rahman, MD,^a Islam Y. Elgendy, MD^j

ABSTRACT

OBJECTIVES The aim of this study was to examine the efficacy and safety of fractional flow reserve (FFR)-guided versus angiography-guided approaches for nonculprit stenosis among patients with acute ST-segment elevation myocardial infarction (STEMI) and multivessel disease.

BACKGROUND The optimal strategy to guide revascularization of nonculprit stenosis among patients with STEMI and multivessel disease remains uncertain.

METHODS Electronic databases were searched for randomized trials evaluating the outcomes of culprit-only revascularization, angiography-guided complete revascularization (CR), or FFR-guided CR. A pairwise meta-analysis comparing CR versus culprit-only revascularization and a network meta-analysis comparing the different revascularization techniques were conducted. The primary outcome was major adverse cardiac events (MACE).

RESULTS The analysis included 11 trials with 8,195 patients. CR (ie, angiography-guided or FFR-guided CR) was associated with a lower incidence of MACE (odds ratio [OR]: 0.46; 95% CI: 0.35 to 0.59), cardiovascular mortality (OR: 0.63; 95% CI: 0.41 to 0.98), recurrent myocardial infarction (OR: 0.67; 95% CI: 0.48 to 0.95), and repeat ischemia-driven revascularization (OR: 0.26; 95% CI: 0.19 to 0.35). Network meta-analysis demonstrated that the incidence of MACE was lower with both angiography-guided CR (OR: 0.43; 95% CI: 0.31 to 0.58) and FFR-guided CR (OR: 0.52; 95% CI: 0.35 to 0.78) compared with a culprit-only approach, while there was no difference in risk for MACE between angiography-guided and FFR-guided CR (OR: 0.81; 95% CI: 0.51 to 1.29).

CONCLUSIONS Among patients with STEMI and multivessel disease, CR, with angiographic or FFR guidance for nonculprit stenosis, was associated with lower incidence of adverse events compared with culprit-only revascularization. FFR-guided CR was not superior to angiography-guided CR in reducing the incidence of adverse events. Future studies investigating other tools to risk-stratify nonculprit stenoses are encouraged. (J Am Coll Cardiol Intv 2022;15:656-666)
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From the ^aDivision of Cardiology, Baylor College of Medicine, Houston, Texas, USA; ^bDepartment of Internal Medicine, University of Texas Medical Branch, Galveston, Texas, USA; ^cDepartment of Internal Medicine, Florida Atlantic University, Boca Raton, Florida; ^dDepartment of Internal Medicine, Lincoln Medical Center, New York, New York, USA; ^eDepartment of Internal Medicine, Banner University Medical Center, Phoenix, Arizona, USA; ^fDepartment of Cardiovascular Medicine, University of Texas Medical Branch, Galveston, Texas, USA; ^gDepartment of Internal Medicine, Cleveland Clinic, Cleveland, Ohio, USA; ^hKeele Cardiovascular Research Group, Centre for Prognosis Research, Keele University, Keele, United Kingdom; ⁱDepartment of Cardiology, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom; and the ^jDepartment of Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar. *Drs Elbadawi and Dang have contributed equally to this work.

Data indicate that approximately 50% of patients undergoing primary percutaneous coronary intervention (PCI) have significant multivessel coronary artery disease.¹ Several randomized controlled trials (RCTs) have demonstrated that a strategy of complete revascularization (CR) for significant nonculprit stenoses in patients without cardiogenic shock, either at the time of the index procedure or as a staged procedure, is superior to a culprit-only strategy in reducing the risk for cardiovascular events, including cardiac mortality and myocardial infarction (MI).²⁻⁴ Society guidelines recommend a CR strategy for significant nonculprit stenoses among patients with multivessel disease not in cardiogenic shock.^{5,6}

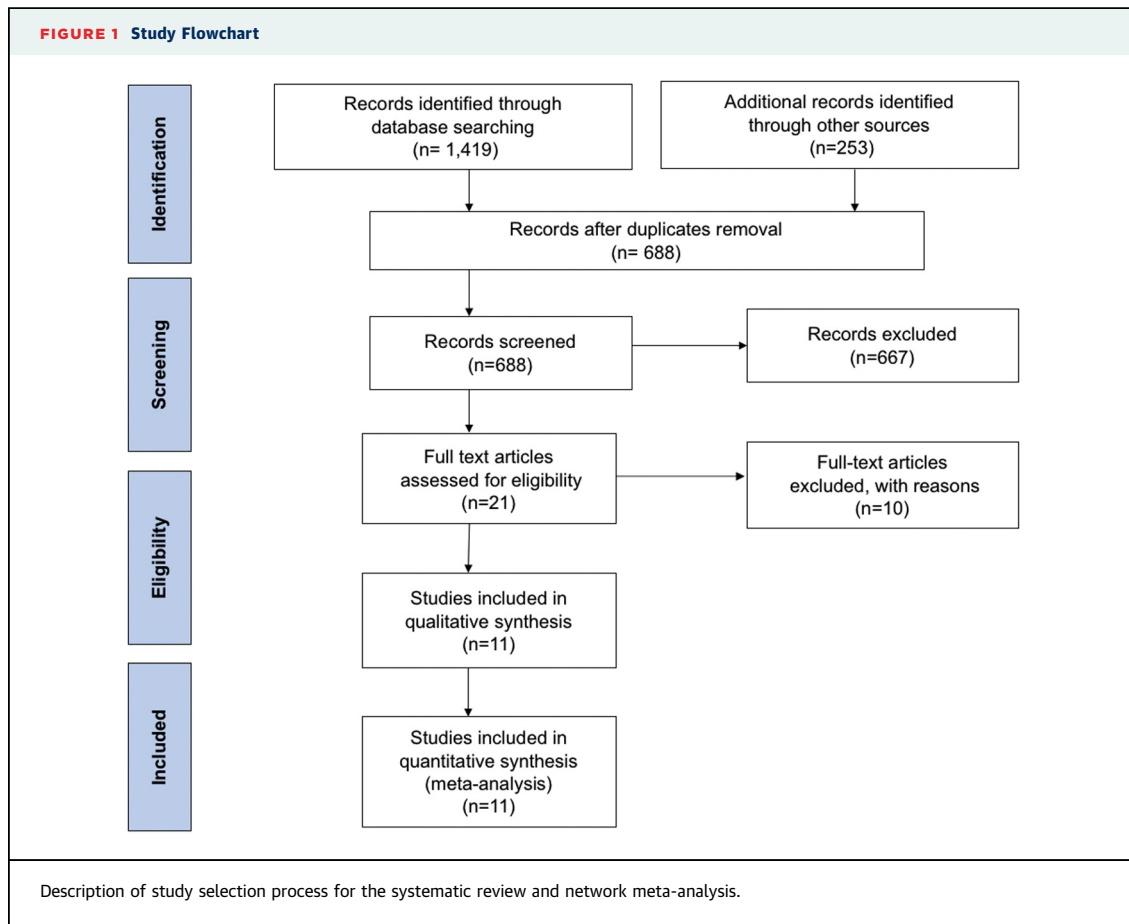
Among patients with chronic coronary syndromes, fractional flow reserve (FFR) has been shown to improve outcomes in guiding revascularization decisions, but the benefit of an FFR-guided strategy in the context of ST-segment elevation MI (STEMI) is not well defined.⁷ Prior RCTs primarily evaluated an FFR-guided or angiography-guided strategy

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in the context of STEMI and multivessel disease, and either strategy reduced adverse events compared with a culprit-only strategy. The recent FLOWER-MI (Flow Evaluation to Guide Revascularization in Multi-Vessel ST-Elevation Myocardial Infarction) RCT evaluated the merits of an

**ABBREVIATIONS
 AND ACRONYMS**

- CR** = complete revascularization
- FFR** = fractional flow reserve
- MACE** = major adverse cardiac event(s)
- MI** = myocardial infarction
- PCI** = percutaneous coronary intervention
- RCT** = randomized controlled trial
- STEMI** = ST-segment elevation myocardial infarction



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 [Author Center](#).

Manuscript received September 17, 2021; revised manuscript received December 2, 2021, accepted January 4, 2022.

TABLE 1 Baseline Characteristics of the Included Studies

Study	Year	Culprit-Only PCI, n	Angiography-Guided, n	FFR-Guided, n	Index PCI (% Within CR)	Index Hospitalization, Delayed PCI (% Within CR)	Staged After Discharge (% Within CR)	DES %	Median Follow-Up Duration, months	
FLOWER-MI ⁸	2021		577	586	4%	96%	-	FFR-guided CR Angio-guided CR	98.8% 98.2%	36
COMPLETE ²	2019	2,025	2016	-	-	67.10%	32.90%	Culprit only PCI Angio-guided CR	86.1% 86.4	36
COMPARE ACUTE ³	2017	590	-	295	83.40%	16.60%	-	Culprit only PCI FFR-guided CR	96.1% IRA: 95.4%, non-IRA: 96.8%	12
Hamza <i>et al.</i> ¹⁹	2016	50	50	-	42%	58%	-	Culprit only PCI Angio-guided CR	100% 100%	6
CVLPRIT ²²	2015	146	150	-	69.8%	30.2%	-	Culprit only PCI Angio-guided CR	90.7% 95.9%	12
DANAMI 3 PRIMULTI ²¹	2015	313	-	314	-	100%	-	Culprit only PCI FFR-guided CR	93% 95%	27
PRAGUE-13 ¹⁶	2015	108	106	-	-	-	100%	Culprit only PCI Angio-guided CR	NA NA	38
PRAMI ¹⁵	2013	231	234	-	100%	-	-	Culprit only PCI Angio-guided CR	58% 63%	23
Ghani <i>et al.</i> ²⁰	2012	41	-	80	-	-	100%	Culprit only PCI FFR-guided CR	17.10% 22.50%	36
Politi <i>et al.</i> ¹⁷	2010	84	130	-	50%	-	50%	Culprit only PCI Angio-guided CR	11.9% 8.5%	30
HELP-AMI ¹⁸	2004	17	52	-	100%	-	-	Culprit only PCI Angio-guided CR	100% 100%	12

CR = complete revascularization; DES = drug-eluting stent(s); FFR = fractional flow reserve; IRA = infarct related artery; PCI = percutaneous coronary intervention.

FFR-guided strategy compared with an angiography-guided strategy for nonculprit stenosis and demonstrated that an FFR-guided strategy did not reduce the risk for the primary outcome of all-cause mortality, MI, or urgent revascularization; however, the CIs for the primary outcome as well as the individual outcomes were wide.⁸ As such, the optimal strategy to guide revascularization of nonculprit stenosis remains uncertain. Accordingly, we aimed to perform a comprehensive network meta-analysis of RCTs to compare FFR- and angiography-guided strategies for nonculprit stenoses among patients with STEMI and multivessel disease.

METHODS

DATA SOURCES AND SEARCH STRATEGY. A computerized search of the MEDLINE, Embase, and Cochrane databases without language restrictions was performed through September 2021, using the terms “myocardial infarction,” “culprit,” “fractional flow reserve,” “angiography,” “multivessel,” and “percutaneous coronary intervention” separately and in combination to identify any RCTs that evaluated the outcomes with culprit-only, FFR-guided CR or

angiography-guided CR among patients with STEMI and multivessel disease. A similar search was also conducted for abstracts of the major scientific sessions (American College of Cardiology, European Society of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions) up to September 2021. The reference lists of the retrieved studies as well as ClinicalTrials.gov were screened for any pertinent studies not retrieved through the primary search. This meta-analysis was conducted in accordance with the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses guidelines⁹ ([Supplemental Table 1](#)) and was registered at PROSPERO ([CRD42021270809](#)). This study was exempted from Institutional Review Board oversight, as it was a study-level meta-analysis.

SELECTION CRITERIA. RCTs that compared clinical outcomes with culprit-only, FFR-guided CR or angiography-guided CR among patients with acute STEMI and multivessel disease were included. For studies with multiple reports, we used data from the longest available follow-up. We excluded non-randomized trials and trials that did not report clinical outcomes.

DATA EXTRACTION. Two independent investigators (A.T.D. and M.A.) extracted the study design, baseline characteristics, intervention strategies, and clinical outcomes. Discrepancies among investigators were resolved by consensus.

OUTCOMES. The primary outcome of the study was the composite of major adverse cardiac events (MACE). The definition of MACE in each study is reported in [Supplemental Table 2](#). The secondary outcomes included all-cause mortality, cardiovascular mortality, recurrent MI (including any recurrent MI, spontaneous MI, and periprocedural MI) ([Supplemental Table 3](#)), repeat ischemia-driven (or urgent) revascularization, and stent thrombosis. Stent thrombosis events were defined in accordance with the Academic Research Consortium criteria.¹⁰

ASSESSMENT OF THE QUALITY OF THE INCLUDED STUDIES. The quality of the included trials was evaluated using the Cochrane risk assessment tool for bias, which comprises 7 criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.¹¹ On the basis of the fulfillment of these criteria, studies were classified as low risk, unclear risk, or high risk for bias.

STATISTICAL ANALYSIS. Outcomes were assessed using an intention to treat analysis. Pairwise meta-analysis was conducted to compare culprit-only versus CR (ie, angiography-guided or FFR-guided) strategies. A network meta-analysis was performed to compare culprit-only revascularization, FFR-guided CR, and angiography-guided CR. Data were pooled using a random-effects model. Inconsistency was examined by comparing the deviance residuals and deviance information criterion statistics in fitted consistency and inconsistency models from the entire network on each node. Summary estimates were reported as odds ratios (ORs) and corresponding 95% CIs. Statistical heterogeneity across trials was assessed using I^2 statistics, with I^2 values <25%, 25% to 50%, and >50% considered to indicate low, moderate, and high degrees of heterogeneity, respectively.^{12,13} Publication bias was evaluated using the Egger test.¹⁴ The following sensitivity analyses for the primary outcome were conducted: 1) excluding studies with high risk of bias; 2) including studies with consistent definition of MACE (ie, composite of all-cause mortality, recurrent MI, or repeat ischemia-driven revascularization); and 3) excluding studies that used predominantly bare-metal stents. To account for the variation in follow-up duration among

the studies, a secondary analysis was also performed for the primary outcome using the HR and corresponding 95% CI from each trial. *P* values were 2-tailed and considered to indicate statistical significance if ≤ 0.05 in all analyses. All analyses were conducted using RStudio with the netmeta and meta packages (RStudio).

RESULTS

INCLUDED STUDIES. The study flow diagram is outlined in [Figure 1](#). The final analysis included 11 RCTs with a total of 8,195 patients.^{2,3,8,15-22} The included studies analyzed culprit-only PCI (n = 3,605), angiography-guided CR (n = 3,315), or FFR-guided CR (n = 1,275) ([Supplemental Figure 1](#), [Supplemental Table 4](#)). The weighted mean follow-up duration was 25.6 months. The characteristics of the included studies are presented in [Table 1](#). Drug-eluting stents were less frequently used in the earlier studies. The timing of nonculprit PCI was variable across the different studies. Nonculprit PCI was predominantly performed during the index PCI procedure in the HELP AMI (Hepacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction) (100%) and PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) (100%) trials, as a staged PCI procedure before hospital discharge in the DANAMI-3–PRIMULTI (Primary PCI in Patients With ST-elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization) (100%) and FLOWER-MI ($\approx 96\%$) trials, as a staged PCI procedure postdischarge in the study of Ghani et al and PRAGUE-13 (Multivessel Coronary Disease Diagnosed at the Time of Primary PCI for STEMI: Complete Revascularization Versus Conservative Strategy), and a mixture of different timings in the remaining studies.^{8,16-21} The characteristics of patients in the included trials are outlined in [Table 2](#). The weighted mean age was 62.6 years. The studies predominantly enrolled male patients. Hamza et al¹⁹ exclusively included patients with diabetes. Nonculprit interventions for the left main coronary artery were performed in a minor proportion of patients.

The quality of included studies is outlined in [Supplemental Table 5](#). All studies were open label. For HELP AMI¹⁸ and Ghani et al,²⁰ blinded outcome assessment could not be ascertained. Regarding the other risk for bias criteria, all included studies were deemed to be at low risk of bias.

PAIRWISE META-ANALYSIS. Compared with culprit-only PCI, CR (ie, angiography-guided or FFR-guided

TABLE 2 Baseline Characteristics of Patients in the Included Trials

Study	Intervention	Age, y ^a	Male, %	Tobacco Use, %	HTN, %	DM, %	Killip Class ≥ 2, %	Nonculprit Lesion Is LMCA, %
FLOWER-MI ⁸	FFR-guided CR	62.5 ± 11.0	85	40.1	43.2	18.3	6.7	1.2
	Angiography-guided CR	61.9 ± 11.4	81.1	36.4	45.4	14.2	5.3	1.6
COMPLETE ²	Culprit-only PCI	62.4 ± 10.7	79.1	38.9	50.7	19.9	10.9	0.1
	Angiography-guided CR	61.6 ± 10.7	80.5	40.6	48.7	19.1	10.6	0.4
Compare-Aute ³	Culprit-only PCI	61 ± 10	76.3	48.7	47.8	15.9	5.1	0.0
	FFR-guided CR	62 ± 10	79.0	40.8	46.1	14.6	5.1	0.4
Hamza et al ¹⁹	Culprit-only PCI	52.2 ± 10.6	86	78	36	100	0	NA
	Angiography-guided CR	56.4 ± 11.5	82	72	26	100	2	NA
CvLPRIT ²²	Culprit-only PCI	65.3 ± 11.9	76.7	26.8	36.4	14.3	9.4	1.4
	Angiography-guided CR	64.6 ± 11.2	85.3	34.3	36.6	12.9	6.8	0.7
DANAMI-3—PRIMULTI ²¹	Culprit-only PCI	63	81	48	47	13	6	NA
	FFR-guided CR	64	80	51	41	9	7	NA
PRAGUE-13 ¹⁶	Culprit-only PCI	NA	NA	NA	NA	NA	NA	NA
	Angiography-guided CR	NA	NA	NA	NA	NA	NA	NA
PRAMI ¹⁵	Culprit-only PCI	62 (33-90)	81	45	40	21	NA	NA
	Angiography-guided CR	62 (32-92)	76	50	40	15	NA	NA
Ghani et al ²⁰	Culprit-only PCI	61 ± 11	80.5	47.5	42.5	5.0	2.4	NA
	FFR-guided CR	62 ± 10	80	44.2	26.3	6.3	6.3	NA
Politi et al ¹⁷	Culprit-only PCI	66.5 ± 13.2	76.2	NA	59.5	23.8	NA	NA
	Angiography-guided CR	64.3 ± 11.4	78.5	NA	56.9	16.2	NA	NA
HELP AMI ¹⁸	Culprit-only PCI	65.3 ± 7.4	84.6	81.0	58.8	41.2	18.8	NA
	Angiography-guided CR	63.5 ± 12.4	88.2	66.6	36.5	11.5	20.0	NA

^aValues are mean ± SD or median (IQR).
DM = diabetes mellitus; HTN = hypertension; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; NA = not available; RCA = right coronary artery; other abbreviations as in [Table 1](#).

CR) was associated with a lower incidence of MACE (10.7% vs 19.4%; OR: 0.46; 95% CI: 0.35 to 0.59; $I^2 = 52\%$) ([Figure 2](#)). Inspection of the funnel plot suggested no evidence of publication bias (Egger test $P = 0.89$) ([Supplemental Figure 2](#)). The secondary analysis using HRS showed consistent findings ([Supplemental Figure 3](#)). Similar findings were also demonstrated in the 3 sensitivity analyses: 1) excluding studies with unclear risk of bias (OR: 0.43; 95% CI: 0.33 to 0.55)^{18,20}; 2) studies with consistent definition of MACE (ie, all-cause mortality, recurrent MI, or repeat ischemia-driven revascularization) (OR: 0.46; 95% CI: 0.28 to 0.76)^{2,3,8,15-22}; and 3) excluding studies with predominant use of bare-metal stents (OR: 0.45; 95% CI: 0.36 to 0.58). Meta-regression analysis did not reveal any evidence of effect modification for MACE with anterior STEMI ($P = 0.25$), procedural time ($P = 0.18$), or contrast volume ($P = 0.49$) ([Supplemental Figure 4](#)). Compared with culprit-only PCI, CR was associated with a lower incidence of cardiovascular mortality (OR: 0.63; 95% CI: 0.41 to 0.98; $I^2 = 23\%$), repeat revascularization (OR: 0.26; 95% CI: 0.19 to 0.35; $I^2 = 39\%$), and any recurrent MI (RR: 0.67; 95% CI: 0.48 to 0.95; $I^2 = 27\%$)

([Figure 2](#)). Subgroup analysis according to type of recurrent MI showed that CR was associated with lower incidence of spontaneous MI (OR: 0.59; 95% CI: 0.46 to 0.75; $I^2 = 0\%$), but not periprocedural MI (OR: 1.01; 95% CI: 0.61 to 1.68; $I^2 = 0\%$), compared with culprit-only PCI ([Supplemental Figure 5](#)). There was no difference between culprit-only and CR approaches in the incidence of all-cause mortality (OR: 0.88; 95% CI: 0.68 to 1.14; $I^2 = 5\%$) or stent thrombosis (OR: 1.47; 95% CI: 0.82 to 2.61; $I^2 = 0\%$) ([Central Illustration, Figure 2](#)).

NETWORK META-ANALYSIS. Compared with culprit-only approach, both angiography-guided CR (OR: 0.43; 95% CI: 0.31 to 0.58) and FFR-guided CR (OR: 0.52; 95% CI: 0.35 to 0.78) were associated with lower incidence of MACE. There was no difference in the incidence of MACE when comparing angiography-guided versus FFR-guided CR (OR: 0.81; 95% CI: 0.51 to 1.29) ([Central Illustration](#)). The secondary analysis using HRS also showed a lower incidence of MACE with either angiography-guided CR or FFR-guided CR compared with culprit-only PCI ([Supplemental Figure 3](#)). Sensitivity analyses

TABLE 2 Continued

Nonculprit Lesion Is LAD, %	Nonculprit Lesion Is Circumflex, %	Nonculprit Lesion Is RCA, %	Anterior Infarct, %	Mean Procedural Duration, min ^a	Mean Contrast Volume, mL ^a
59.9	40.8	30.5	29.8	Index, 31 (21-45); staged, 35 (22-50)	Index, 148 (109.5-180); staged, 110 (71.8-170)
54.8	38.5	29.8	34.6	Index, 32 (20-46); staged, 30 (20-44)	Index, 140 (110-171.5); staged, 110 (80-150)
41.2	35.6/	23.2	NA	NA	NA
38.0	36.4	25.3	NA	NA	NA
42.1	33.9	24.1	34.9	59 ± 28	202 ± 75
40.8	33.0	26.2	35.6	65 ± 31	224 ± 104
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
48.0	13.7	30.8	35.6	41 (30-55.5)	190 (150-250)
42.6	13.3	31.3	36.0	55 (38-74)	250 (190-330)
NA	NA	NA	36	42	170
NA	NA	NA	33	76	280
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	39/29	45 (32-60)	200 (150-260)
NA	NA	NA	29	63 (46-80)	300 (210-380)
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	41.7	NA	NA
NA	NA	NA	45.4	NA	NA
NA	NA	NA	NA	53 ± 21	242 ± 102
NA	NA	NA	NA	69 ± 32	341 ± 163

excluding studies with unclear risk of bias,^{18,20} as well as those with predominant use of bare-metal stents,^{17,18,20} showed similar results. Similar findings were also observed on the sensitivity analysis with a consistent definition of MACE (ie, all-cause mortality, recurrent MI, or repeat ischemia-driven revascularization)^{2,3,8,15-22} (Supplemental Figure 6).

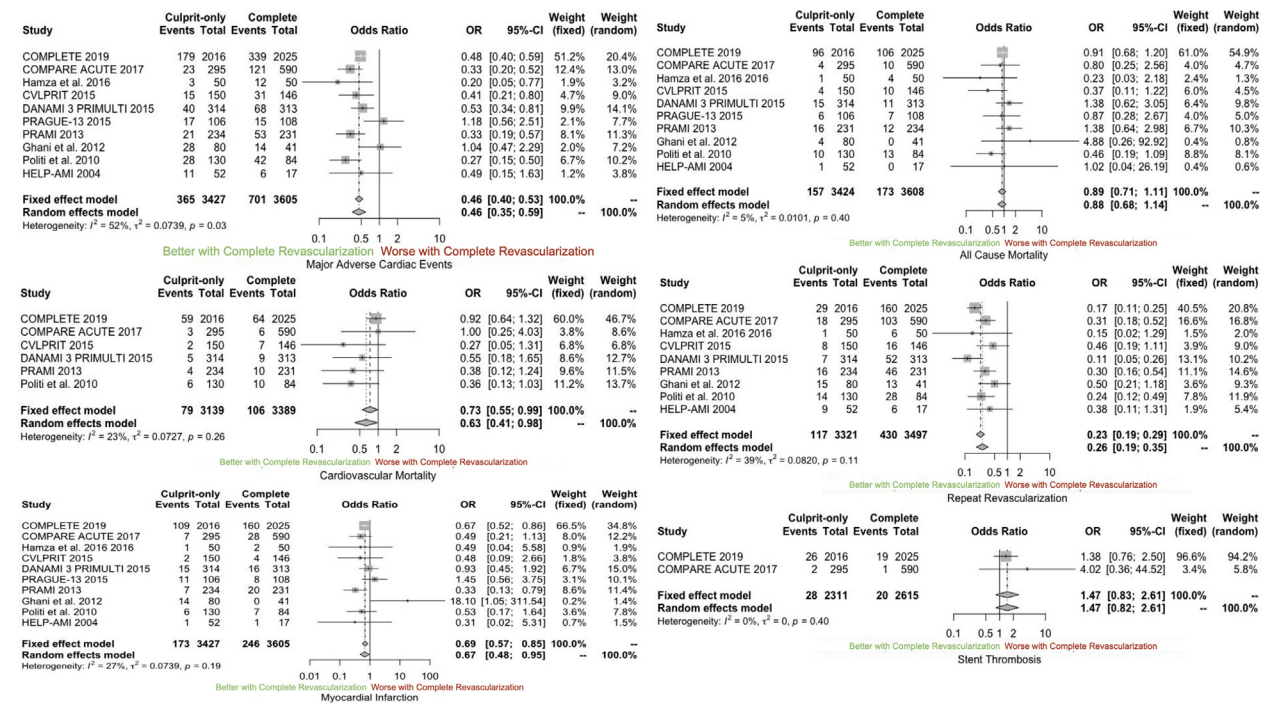
Compared with culprit-only PCI, angiography-guided CR was associated with a lower incidence of any recurrent MI (OR: 0.60; 95% CI: 0.40 to 0.89) and spontaneous MI but no difference in periprocedural MI. There were no differences between FFR-guided CR and culprit-only PCI in the incidence of any recurrent MI (OR: 0.90; 95% CI: 0.51 to 1.57), spontaneous MI, or periprocedural MI (Table 3). Compared with a culprit-only approach, angiography-guided CR (OR: 0.24; 95% CI: 0.17 to 0.34) and FFR-guided CR (OR: 0.29; 95% CI: 0.19 to 0.45) were associated with lower incidence of repeat revascularization. There were no differences between the 3 revascularization approaches in the other outcomes (Table 3).

DISCUSSION

In this network meta-analysis of 11 RCTs including 8,195 patients, we evaluated the outcomes of different revascularization approaches among

patients presenting with STEMI and multivessel disease. The salient study findings were as follows: 1) CR with either angiographic or FFR guidance was associated with a lower incidence of MACE, cardiovascular mortality, recurrent MI, and repeat ischemia-driven revascularization compared with a culprit-only revascularization approach; 2) network meta-analysis showed no significant difference between angiography-guided CR and FFR-guided CR in the incidence of MACE as well as all secondary endpoints; 3) angiography-guided CR was associated with a lower incidence of MACE and any recurrent MI, while FFR-guided CR was associated with a lower incidence of MACE, with no differences in the other secondary endpoints, compared with a culprit-only revascularization approach.

Prior meta-analyses have demonstrated the superiority of a CR approach in improving clinical outcomes among patients with STEMI and multivessel disease.^{4,23} A recent meta-analysis of RCTs demonstrated a reduction in the composite of cardiovascular mortality or recurrent MI with complete revascularization versus culprit-only approaches. However, there was no difference between an angiography-guided or FFR-guided approach on subgroup analysis that included 4 trials (3 evaluating an angiography-guided approach and 1 using an

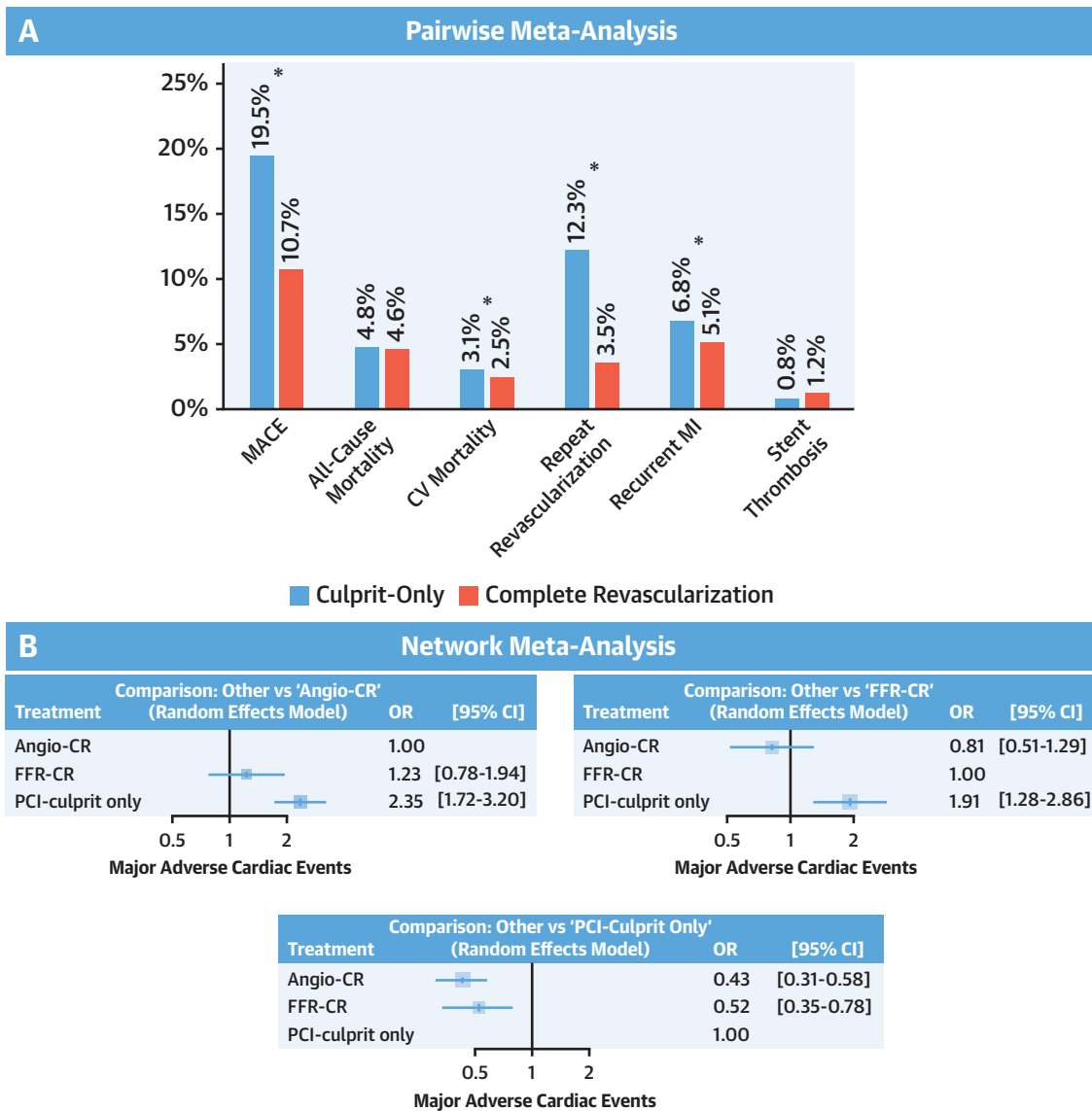
FIGURE 2 Pairwise Meta-Analysis Comparing Complete Revascularization Versus Culprit-Only Approaches

Forest plot for the risk for major adverse cardiac events, all-cause mortality, cardiovascular mortality, any recurrent myocardial infarction, repeat ischemia-driven revascularization, and stent thrombosis. COMPARE ACUTE = Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD; COMPLETE = Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI; CVLPRIT = Complete Versus 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; PRAGUE-13 = Multivessel Coronary Disease Diagnosed at the Time of Primary PCI for STEMI: Complete Revascularization Versus Conservative Strategy; PRAMI = Preventive Angioplasty in Acute Myocardial Infarction.

FFR-guided approach).²³ Consistent with these findings, this analysis showed that a CR approach with either angiographic guidance or FFR-guidance was associated with a lower incidence of MACE, as well as cardiovascular mortality and recurrent MI (driven by lower incidence of spontaneous MI).²³ By performing a network meta-analysis including the recent FLOWER-MI trial, we expanded on these prior meta-analyses by comparing the different revascularization approaches to guide the decision regarding the nonculprit stenosis. We demonstrated that CR with either angiographic or FFR guidance was associated with a lower incidence of MACE compared with culprit-only revascularization. There were no significant differences between angiography-guided and FFR-guided CR in the other outcomes. However, angiography-guided CR was associated with a lower incidence of MACE and any recurrent MI, while FFR-guided CR was associated with a lower incidence of MACE compared with culprit-only revascularization.

In this analysis, FFR-guided CR failed to show better outcomes compared with angiography-guided CR. This is in contrast to the superiority of FFR-guidance for revascularization of chronic coronary syndromes.^{5,24,25} Although FFR-guidance reduced the number of stents in the FLOWER-MI trial, the risk of adverse events including recurrent MI was numerically higher in the FFR arm.⁸ In our network meta-analysis, we demonstrated that an angiography-guided approach for CR might be associated with lower incidence of recurrent MI compared with culprit-only stenosis, but a similar association was not observed with an FFR-guided approach. It is plausible that the different physiological milieu during STEMI could have contributed to the lack of benefits with FFR-guidance compared with chronic coronary syndromes.²⁶ FFR is mostly reliable during maximal microvascular dilation. Prior reports have described metabolic changes in nonischemic territories during myocardial ischemia that are mediated

CENTRAL ILLUSTRATION Main Study Findings



Elbadawi A, et al. *J Am Coll Cardiol Intv.* 2022;15(6):656-666.

(A) Incidence of the outcomes with complete revascularization versus culprit-only approaches. *Statistical significance. (B) Network meta-analysis, for major adverse cardiac events comparing culprit-only approach, angiography-guided complete revascularization, and fractional flow reserve (FFR)-guided complete revascularization (CR). CV = cardiovascular; PCI = percutaneous coronary intervention.

by increases in catecholamine levels resulting in increased oxygen requirements, lower glycogen content, reduction of myocardial oxidation-reduction enzymes, and disruption of mitochondrial activity.²⁷ Animal studies have demonstrated functional abnormalities in nonischemic regions during acute ischemia.²⁸ These metabolic and functional disturbances might impair microvascular optimization for FFR measurement during STEMI. While FFR assesses

functional significance, the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial demonstrated that non-culprit lesions that led to MACE were frequently mild on angiographic assessment and were characterized by a large plaque burden, the presence of thin-cap fibroatheromas, or minimal luminal area $\leq 4 \text{ mm}^2$ using intravascular ultrasound imaging, suggesting that fibroatheroma morphology might be more

TABLE 3 Network Meta-Analysis Comparing the Clinical Outcomes

	Culprit-Only PCI	Angiographic-Guided CR	FFR-Guided CR
All-cause mortality			
Culprit-only PCI	–	0.82 (0.65-1.03)	1.04 (0.61-1.76)
Angiographic-guided CR	1.22 (0.97-1.55)	–	1.27 (0.73-2.19)
FFR-guided CR	0.96 (0.57-1.64)	0.79 (0.46-1.36)	–
Cardiovascular mortality			
Culprit-only PCI	–	0.56 (0.31-1.02)	0.70 (0.25-1.97)
Angiographic-guided CR	1.79 (0.98-3.26)	–	1.26 (0.38-4.15)
FFR-guided CR	1.42 (0.51-3.99)	0.79 (0.24-2.62)	–
Repeat revascularization			
Culprit-only PCI	–	0.24 (0.17-0.34)	0.29 (0.19-0.45)
Angiographic-guided CR	4.18 (2.92-5.97)	–	1.21 (0.74-1.97)
FFR-guided CR	3.46 (2.23-5.38)	0.83 (0.51-1.35)	–
All recurrent MI			
Culprit-only PCI	–	0.60 (0.40-0.89)	0.90 (0.51-1.57)
Angiographic-guided CR	1.67 (1.12-2.49)	–	1.50 (0.82-2.75)
FFR-guided CR	1.11 (0.64-1.95)	0.67 (0.36-1.22)	–
Spontaneous recurrent MI			
Culprit-only PCI	–	0.56 (0.43-0.73)	0.73 (0.44-1.21)
Angiographic-guided CR	1.79 (1.37-2.34)	–	1.30 (0.76-2.23)
FFR-guided CR	1.37 (0.83-2.28)	0.77 (0.45-1.31)	–
Peri-procedural recurrent MI			
Culprit-only PCI	–	0.82 (0.26-2.57)	1.28 (0.31-5.28)
Angiographic-guided CR	1.22 (0.39-3.85)	–	1.57 (0.76-2.23)
FFR-guided CR	0.78 (0.19-3.22)	0.64 (0.14-2.85)	–
Stent thrombosis			
Culprit-only PCI	–	1.37 (0.79-2.38)	1.24 (0.37-4.14)
Angiographic-guided CR	0.73 (0.42-1.27)	–	0.91 (0.29-2.81)
FFR-guided CR	0.81 (0.24-2.68)	1.10 (0.36-3.41)	–

Values are odds ratio (95% CI). The top row represents the comparator.
CR = complete revascularization; FFR = fractional flow reserve; MI = myocardial infarction; PCI = percutaneous coronary intervention.

relevant than functional significance on FFR assessment.²⁹ This is particularly relevant in our analysis, which showed that angiography-guided CR was associated with a reduction in the incidence of future spontaneous MI compared with culprit-only PCI, whereas FFR-guidance was not. Moreover, the FLOWER-MI trial showed that patients who had ≥ 1 PCI had lower clinical event rates at 1 year compared with patients with deferred PCI.³⁰ Conversely, data from the Compare-Acute (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD) study showed comparable MACE rates between patients who underwent FFR-guided CR and those with deferred PCI.³ Collectively, the available data do not support the routine use of an FFR-guided approach when planning CR in the setting of STEMI, and it might cause undue extra cost and procedural time.

STUDY LIMITATIONS. First, the direct comparison between angiography- and FFR-guided CR was available in only 1 RCT. Second, the timing of CR varied across the studies (ie, index PCI, staged PCI during the same admission, or after discharge). Third, the

definition of MACE was not consistent among the studies. A sensitivity analysis including studies with uniform definition of MACE (ie, all-cause mortality, recurrent MI, or repeat revascularization) for both the pairwise and network meta-analyses showed consistent findings. Fourth, the definition of recurrent MI was also variable among the studies, so we performed an analysis for any recurrent MI and a subgroup analysis according to the type of MI (ie, spontaneous or periprocedural MI). Fifth, the duration of follow-up was variable among the studies, so we performed a secondary analysis using HRs and corresponding 95% CIs from the individual studies, which showed similar results as the primary analysis. Sixth, some of the older studies used bare-metal stents. Sensitivity analysis excluding trials with predominant use of bare-metal stents was consistent with the primary analysis. Seventh, exploring the outcomes of patients with deferred PCI on the basis of FFR values would have provided further insight regarding the comparison between FFR-guided and angiography-guided CR. However, data regarding outcomes with deferred PCI were reported in only 2 RCTs, so further analyses could not be performed. Finally, the lack of patient-level data precluded further analyses to determine the subgroup that would derive the most benefit.

CONCLUSIONS

In this network meta-analysis of RCTs, CR with either angiographic or FFR guidance was associated with a lower incidence of adverse events, including cardiovascular mortality and recurrent MI, compared with a culprit-only revascularization approach in patients with STEMI and multivessel disease. There were no differences between FFR-guided and angiography-guided CR in all clinical endpoints. The findings of this meta-analysis do not support the routine use of FFR to guide revascularization decisions for non-culprit stenoses among patients with STEMI and multivessel disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Elgendy has received research grants from Caladrius Biosciences, unrelated to the present work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Islam Y. Elgendy, Weill Cornell Medicine-Qatar Education City, QatarFoundation, PO Box 24144, Doha, Qatar. E-mail: iyelgendy@gmail.com. Twitter: [@islamelgendy83](https://twitter.com/islamelgendy83).

PERSPECTIVES

WHAT IS KNOWN? A significant proportion of patients with STEMI have significant multivessel disease. The COMPLETE (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI) trial demonstrated that a CR approach reduces the risk of the composite of cardiovascular mortality or recurrent MI.

WHAT IS NEW? Compared with culprit-only revascularization, CR, with either angiographic or FFR-guidance, was associated with a lower incidence of MACE, cardiovascular mortality, recurrent MI, and repeat ischemia-driven revascularization. Network meta-analysis showed no significant difference between angiography-guided CR

and FFR-guided CR in the incidence of MACE as well as the other secondary endpoints. Network meta-analysis also demonstrated that angiography-guided CR was associated with a lower incidence of MACE and recurrent MI, while FFR-guided CR was associated with a lower incidence of MACE, with no differences in the other secondary endpoints, compared with culprit-only revascularization.

WHAT IS NEXT? Future studies investigating the role of other tools to risk-stratify nonculprit stenoses are encouraged.

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KEY WORDS angiography, complete revascularization, FFR, multivessel disease, STEMI

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