Meta-Analysis Comparing Fractional Flow Reserve and Angiography-Guided Complete Revascularization of Nonculprit Artery for ST-Elevation Myocardial Infarction

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This study aimed to compare complete revascularization (CR) guided by angiography with a fractional flow reserve (FFR)-guided strategy in patients presenting with ST-segment elevation myocardial infarction (STEMI) and multivessel disease (MVD). CR is preferred to culprit-only revascularization for patients with STEMI and MVD. However, whether FFR-guided CR is superior to angiography-guided CR is unclear in patients presenting with STEMI who have MVD. Randomized controlled trials comparing CR with an FFR- or angiography-guided strategy to culprit-only revascularization in patients with STEMI and MVD were systematically identified. A random-effects network meta-analysis was performed comparing clinical outcomes in the 3 arms. A total of 13 studies with a total of 8,927 patients were included in our analysis. Compared with culprit-only revascularization, angiography-guided CR was associated with a significantly decreased risk of myocardial infarction (MI) (hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.37 to 0.82), all-cause death (HR 0.69, 95% CI 0.49 to 0.97), and cardiovascular death (HR 0.54, 95% CI 0.34 to 0.85) but FFR-guided CR was not (MI: HR 0.77, 95% CI 0.53 to 1.12; cardiovascular death: HR 0.89, 95% CI 0.64 to 1.24; all-cause death: HR 0.93, 95% CI 0.72 to 1.18). The network meta-analysis comparison of angiography- versus FFR-guided CR showed an HR of 0.75 (95% CI 0.50 to 1.11) for all-cause death and an HR of 0.71 (95% CI 0.54 to 1.17) for MI. In conclusion, for patients with MVD presenting with STEMI, angiography-guided CR may provide additional benefits compared with FFR-guided CR. **(Am J Cardiol 2022;183:8−15)**

Primary percutaneous coronary intervention (PCI) of the culprit artery in patients presenting with ST-elevation myocardial infarction (STEMI) is recommended because of its reduction in death, myocardial infarction (MI), stroke, and major bleeding compared with systemic thrombolysis.[1] Multivessel disease (MVD) is present in approximately 50% of patients with STEMI and is associated with increased morbidity and mortality.[2,3] The updated 2021 American guidelines recommend staged PCI of the nonculprit artery in selected patients with STEMI and MVD.[4] This recommendation is based on recent evidence showing that complete revascularization (CR) in these circumstances is beneficial.[5−8] When performing CR, using a fractional flow reserve (FFR) or angiography-guided strategy is highly debatable. With the publication of the first randomized controlled trial (RCT) directly comparing the 2 strategies (FLOWER-MI [Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction]),[9] we aimed to perform network meta-analysis to determine the optimal strategy in

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the assessment of nonculprit lesions in patients with MVD presenting with STEMI.

Methods

We conducted a systematic review and network meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10] The meta-analysis was registered at PROSPERO (CRD42022304387). All RCTs comparing culprit-only revascularization with CR with FFR- or angiography-guided strategy in patients with STEMI and MVD that published or presented at an academic conference were eligible to be included in our analysis. Results were not filtered by the language of publication or sample size, and studies comparing a diagnosis other than STEMI were excluded. An exhaustive literature search of PubMed and EMBASE was performed in July 2021. The search terms were "ST-elevation myocardial infarction," "multivessel disease," "complete," "nonculprit," "revascularization," "intervention," "percutaneous coronary intervention," "angioplasty," and "randomized." A search algorithm for each database is provided in Supplementary Table 1. In addition to articles retrieved by our search strategy, we considered trials obtained from the references in the screened studies, review articles, and previous meta-analyses to be included if deemed appropriate. Two investigators (A.O. and N.B.S.) independently reviewed the published manuscripts and screened abstracts and full-text versions of the studies that met the previously mentioned inclusion criteria. The investigators resolved disagreement by consensus with third-party arbitration. The 2 reviewers (A.O. and N.B.S.) individually extracted the data, including the study design, baseline characteristics, procedural details, and outcomes of interest. Any disagreements among the authors were resolved by consensus with third-party adjudication. The hazard ratio (HR) or risk ratio was extracted for each study.

Two reviewers (A.O. and H.U.) assessed bias risk using the Cochrane Collaboration tool for assessing the risk of bias in RCTs.[11] We used Egger test and funnel plots to assess publication bias.[12] The primary end point of our analysis was all-cause death and secondary end points included MI, trial-defined major adverse cardiovascular (CV) event (MACE), CV death, and revascularization. Our safety outcomes of interest were stroke, major bleeding, and contrast-induced acute kidney injury.

We calculated the HR and associated 95% confidence interval (CI) or risk ratio for each prespecified outcome. The key comparison of the analysis was FFR-guided CR of the nonculprit artery versus angiography-guided CR of the nonculprit artery versus culprit-only revascularization. We performed a random-effects network meta-analysis using the "netmeta" 3.6.2 package (R Foundation for Statistical Computing, Vienna, Austria).[13] Heterogeneity was defined using I^2. The I^2 values were interpreted as follows: values of <25%, 25% to 75%, and >75% corresponded to low, moderate, and high levels of heterogeneity, respectively. In addition, a traditional pairwise meta-analysis was performed for the outcome of all-cause death using Review Manager, version 5.

Results

We identified 1,240 studies through our database search. After removing duplicate results, we selected 904 articles for the title and abstract screening. We excluded 880 irrelevant publications. Of 24 studies that satisfied our full-text screening criteria, 11 were excluded, and 13 were included for the final analysis (Figure 1).[5,9,14–24] A total of 2 trials were excluded because they compared the timing of angiography-guided CR and did not include a culprit-only arm.[25,26]

The study design varied among the trials included. A total of 8 trials used an angiography-guided strategy for CR.[14,16,18,19,21–24] The cut-off for angiographically significant stenosis leading to PCI of the nonculprit artery ranged among these trials from 50% to 80%. Four trials compared FFR-guided CR with a culprit-only strategy.[5,15,17,20] The cut-off value for FFR was 0.80 in all but 1 trial, which used 0.75 (Table 1).[17] The FLOWER-MI trial was the only trial to perform a head-to-head comparison between angiography- and FFR-guided strategy for CR. The timing of nonculprit artery PCI in the CR arms of the trials varied between the index procedure, staged PCI before discharge from the index admission, staged PCI after discharge, or a combination of these strategies.

A total of 8,927 patients were included in our analysis. Tables 1 and 2 include the study and patient characteristics among the 13 trials. The antiplatelet medication at discharge is displayed in Supplementary Table 2. Supplementary Table 3 lists the exclusion criteria and definitions of the individual trial's efficacy and safety outcomes. The evidence network for all-cause mortality is highlighted in Figure 2.

An illustrative table and graph highlighting the risk of bias for the trials in our analysis appear in Supplementary Figure 1. A funnel plot for visual assessment of publication bias is presented in Supplementary Figure 2. The data extracted for the outcomes of interest from each trial are portrayed in Supplementary Table 4. A summary of the network meta-analysis is provided in Table 3. Network meta-analysis showed that compared with culprit-only revascularization, angiography-guided CR was associated with a significant reduction in the risk of MI (HR 0.55, 95% CI 0.37 to 0.82), CV death (HR 0.54, 95% CI 0.34 to 0.85), and all-cause death (HR 0.69, 95% CI 0.49 to 0.97) but FFR-guided CR was not (MI: HR 0.77, 95% CI 0.53 to 1.12; CV death: HR 0.89, 95% CI 0.64 to 1.24; all-cause death: HR 0.93, 95% CI 0.72 to 1.18). (Figures 3 and 4). The network meta-analysis comparison of angiography- versus FFR-guided CR showed an HR of 0.75 (95% CI 0.50 to 1.11) for all-cause death and an HR of 0.71 (95% CI 0.54 to 1.17) for MI (Figure 3). Both angiography and FFR-guided CR significantly reduced the risk of MACE (HR 0.53, 95% CI 0.41 to 0.69; HR 0.57, 95% CI 0.42 to 0.77, respectively) and revascularization (HR 0.43, 95% CI 0.23 to 0.6; HR 0.33, 95% CI 0.22 to 0.5, respectively) compared with culprit-only revascularization (Figure 4). There was no significant heterogeneity in all the primary or secondary outcomes, except for MACE and revascularization, demonstrating moderate heterogeneity (I^2 = 54.2 and 57, respectively) (Supplementary Table 5). Our analysis did not

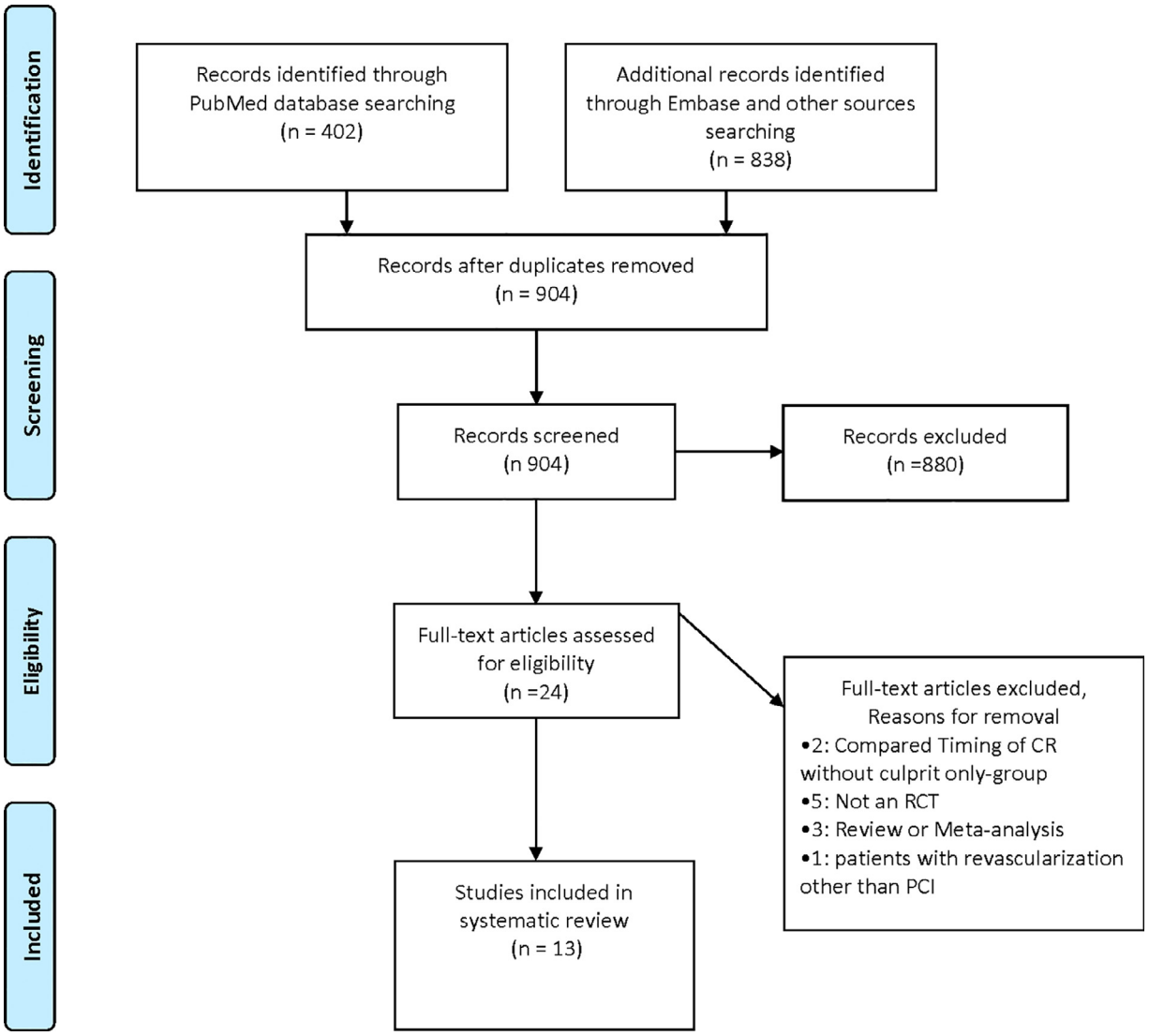

Figure 1. PRISMA flow diagram Outline of the systematic search conducted leading to selection of included studies. CTO = chronic total occlusion; NSTEMI = non-ST elevation myocardial infarction; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

appreciate any inconsistency. Supplementary Figure 3 displays a forest plot of a traditional meta-analysis for the outcome of all-cause death among the 3 groups. There was no statistically significant difference in contrast-induced acute kidney injury, stroke, or major bleeding among the treatment arms (Supplementary Figure 4).

Discussion

The key findings in this network meta-analysis were as follows: (1) angiography-guided CR is associated with a reduction in all-cause death, CV death, MACE, and MI, whereas FFR-guided CR is associated with a reduction in MACE without a difference in the other end points when compared with culprit-only revascularization. (2) There was no significant difference between FFR-guided CR and angiography-guided CR in both efficacy and safety outcomes.

Our analysis is in line with recent meta-analyses, showing a reduction in CV death and MI with CR of nonculprit arteries in patients with STEMI with MVD.[27–29] However, using network meta-analysis with the inclusion of the recent FLOWER-MI trial, we build on the current knowledge by comparing all 3 revascularization strategies primarily used in clinical practice to guide the approach to nonculprit lesions in the context of STEMI. Unique to our analysis is the reduction in all-cause death and MI when angiography-guided CR is performed, and these hard end points are only reduced in the angiography-guided group when both strategies are compared with culprit-only revascularization.

The exact mechanism by which multivessel PCI may improve clinical outcomes in patients with STEMI has not been clearly elucidated. We hypothesize that the benefit seen in our network meta-analysis with the angiography-guided group is due to a lower threshold for stent placement. An optical coherence tomography (OCT) substudy of the COMPLETE trial demonstrated that obstructive nonculprit lesions (>70% visual stenosis) in patients with STEMI more commonly have increased lipid content and other plaque features of vulnerability than nonobstructive lesions.

Table 1
Characteristics of studies included in analysis

Study	Year	Follow up	Patient number	Intervention	Non-culprit vessel definition	FFR use	Outcomes
Angiography-guided CR vs culprit only							
HELP AMI Dimario et al	2004	12m	69	Culprit-only PCI vs angiography-guided CR	No exact % stated	(0)	MACE, all-cause death, MI, revascularization
Politi et al	2010	30m	214	Culprit-only PCI vs angiography-guided CR during the index or staged procedure	>70% stenosis	(0)	MACE, all-cause death, CV death, MI, revascularization
PRAMI Wald et al	2013	23m	465	Culprit-only PCI vs angiography-guided CR during the index procedure	>50% stenosis	(0)	MACE, all-cause death, CV death, MI, revascularization, stroke, major bleeding, CI-AKI
CvLPRIT Gershlick et al	2015	12m	296	Culprit-only PCI vs angiography-guided CR during the index procedure	>70% stenosis in single view or 50% in 2 views	(0)	MACE, all-cause death, CV death, MI, revascularization
PRAGUE 13 Hilnomaz et al	2015	38m	214	Culprit-only PCI vs angiography-guided staged CR (3-40d)	>70% stenosis	(0)	MACE, all-cause death, CV death, MI, stroke
Zhang et. al	2015	24m	428	Culprit-only PCI vs angiography-guided CR	75-90% stenosis	(0)	MACE, all-cause death, CV death, MI, revascularization, re-hospitalization
Hamza et al	2016	6m	100	Culprit-only PCI vs angiography-guided CR during the index procedure or staged (within 72 hours) in patients with diabetes	>80% stenosis	(0)	MACE, all-cause death, MI, revascularization, stroke, major bleeding, CI-AKI
CROSS-AMI Calviño-Santos et. al	2019	12m	306	Culprit only with stress echocardiography−guided revascularization vs angiography-guided CR	>70% stenosis	(0)	MACE, all-cause death, CV death, MI, revascularization
FFR-guided CR vs culprit-only							
Ghani et al	2012	36m	119	Culprit-only PCI vs FFR-guided CR (unless visually severe >90%)	>50% stenosis and FFR ≤0.75	+, FFR ≤0.75	MACE, all-cause death, MI, revascularization
DANAMI-3-PRIMULTI Engstrøm et al	2015	27m	627	Culprit-only PCI vs FFR-guided staged CR (2 days after index)	>50% stenosis, FFR ≤0.80	(+), FFR <0.80	MACE, all-cause death, CV death, MI, revascularization, stroke, major bleeding, CI-AKI
COMPARE-ACUTE Smits et al	2017	36m	885	Culprit-only PCI vs FFR-guided CR during the index procedure	>50% stenosis, FFR ≤0.80	+, FFR <0.80	MACE, all-cause death, CV death, MI, revascularization, stroke, major bleeding
COMPLETE Mehta et al	2019	36m	4041	Culprit-only vs Staged CR either during admission or after discharge (within 45 days)	> 70% stenosis or 50% −69% stenosis with FFR ≤0.80	+, FFR <0.80	MACE, all-cause death, CV death, MI, revascularization, stroke, major bleeding, CI-AKI
FFR-guided CR vs angiography-guided CR							
FLOWER-MI Puymirat et al	2021	12m	1163	Angiography-guided CR vs FFR-guided CR	>50% stenosis or FFR<0.80	+, FFR <0.80	MACE, all-cause death, MI, revascularization

CI-AKI = contrast-induce acute kidney injury; CR= complete revascularization; CV = cardiovascular; FFR = Fractional Flow Reserve; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2
Baseline patient characteristics from included studies

Study	Year	Patient number	Age (years)	Women	DM (%)	HTN (%)	HLD (%)	Current smoker (%)	Previous PCI (%)	3 vessel coronary disease (%)
Angiography-guided CR vs culprit only										
HELP AMI	2004	69	64±11	13%	19%	42%	44%	70%	0.40%	35%
Politi	2010	214	65±12	22%	19%	58%	NA	NA	NA	32%
PRAMI	2013	465	62	22%	18%	40%	NA	48%	NA	36%
CvLPRIT	2015	296	65±12	19%	14%	37%	26%	31%	3%	23%
PRAGUE 13	2015	214	NA	NA	NA	NA	NA	NA	NA	NA
Zhang	2015	428	NA	NA	NA	NA	NA	NA	NA	NA
Hamza	2016	100	56±11.5	16%	100%	31%	45%	75%	7%	31%
CROSS-AMI	2019	306	62±11	16%	14%	44%	NA	43%	NA	43%
FFR-guided CR vs culprit-only										
Ghani	2012	119	62±10	20%	6%	32%	20%	45%	3%	23%
DANAMI-3-PRIMULTI	2015	627	64	19%	11%	44%	NA	50%	NA	31%
Compare-Acute	2017	885	61±10	23%	16%	47%	31%	46%	8%	32%
COMPLETE	2019	4041	62±11	20%	20%	50%	39%	40%	7%	22%
FFR-guided CR vs angiography-guided CR										
FLOWER-MI	2021	1163	62.2±11	17%	16%	44%	40%	38%	9%	23%

Half the patients assessed by OCT had obstructive nonculprit lesions with vulnerable plaque morphology.[30,31] A recent triple vessel OCT study found that the incidence of plaque rupture in nonculprit lesions in patients with STEMI was double that in patients with non-STEMI, suggesting that patients with STEMI are a particularly high-risk group. The benefit of intervening in obstructive nonculprit lesions after primary PCI may come from stenting and stabilizing these vulnerable plaques.[32]

There may be several explanations for why our analysis did not find the FFR-guided CR strategy to be superior to the angiography-guided strategy in the context of STEMI. FFR relies on invoking hyperemia to the epicardial vessels to designate lesions likely causing ischemia and thus would benefit from stent placement. The coronary milieu after a STEMI is highly inflammatory, with the release of neurohormonal factors reducing activation of adenosine receptors and increasing levels of vasoconstrictors.[33,34] Consequently, this may alter the stability of the microcirculation, leading to the blunting of the expected vasodilatory response, overestimation of the FFR, and stent deferral of potentially high-risk lesions.[35] Moreover, the vascular changes affecting hyperemic indexes in the acute phase after a STEMI have been shown to extend past the infarct zone into remote areas perfused by nonculprit lesions and are especially pronounced in patients with large infarcts.[34,36] In a recent study evaluating this phenomenon, FFR values were lower at follow-up, with a mean reduction of 0.03 from the index procedure to 30-day follow-up.[37] This may suggest a role for delaying physiologic measurements to a staged procedure, re-evaluating the exact cut-off for lesions causing ischemia, or combining the use of other physiologic parameters, such as instantaneous wave : free ratio for those lesions with an FFR around 0.80. However, the inconclusive results seen in individual end points with an FFR-guided approach may be due to the lack of power and limited sample size, as evidenced by the limited studies using FFR-guided compared with an angiography-guided approach, wide CIs in end points in the FFR-guided group,

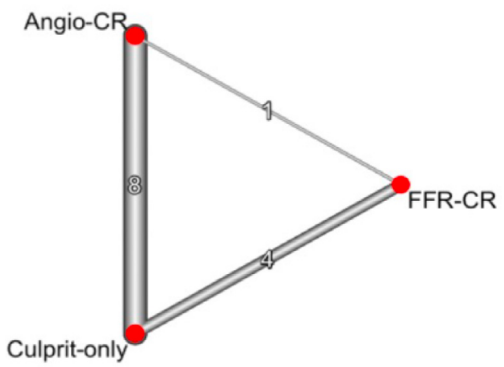

Figure 2. Evidence Network for all-cause death. The width of the lines between each intervention arm correlates with the number of trials available for comparison. Angio = angiography-guided; FFR = fractional flow reserve.

Table 3
Summary of results from network meta-analysis

Outcome	HR (95% CI)
All-cause death	
Angiography-guided CR vs. culprit-only	0.69 (0.49-0.97)
FFR-guided CR vs. culprit-only	0.93 (0.72-1.18)
Angiography-guided CR vs FFR-guided CR	0.74 (0.50-1.11)
MI	
Angiography-guided CR vs. culprit-only	0.55 (0.37-0.82)
FFR-guided CR vs. culprit-only	0.77 (0.52-1.12)
Angiography-guided CR vs FFR-guided CR	0.71 (0.43-1.17)
Cardiovascular death	
Angiography-guided CR vs. culprit-only	0.54 (0.34-0.85)
FFR-guided CR vs. culprit-only	0.89 (0.64-1.24)
Angiography-guided CR vs FFR-guided CR	0.60 (0.34-1.06)
Revascularization	
Angiography-guided CR vs. culprit-only	0.43 (0.30-0.6)
FFR-guided CR vs. culprit-only	0.33 (0.20-0.5)
Angiography-guided CR vs FFR-guided CR	1.28 (0.77-2.10)

CI = confidence interval; HR = hazard ratio; Abbreviations as in Tables 1 and 2.

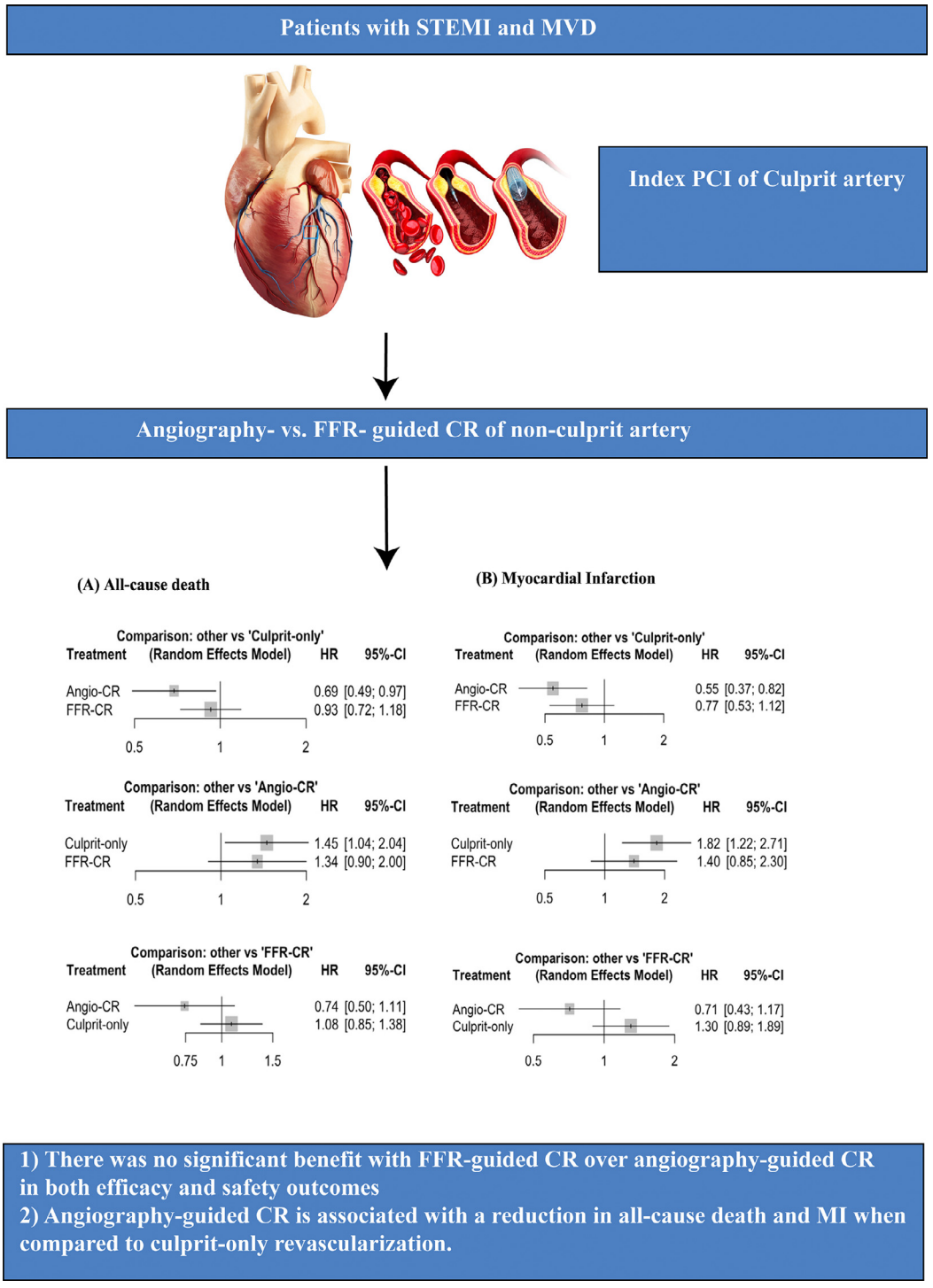

Figure 3. Study Overview and Results of Network Meta-analysis for all-cause death and myocardial infarction Forest plot for the comparisons among each treatment arm for all-cause death and MI. (*A*) all-cause death, (*B*) MI. Angio = angiography-guided.

and an isolated positive effect with an FFR-guided strategy on MACE reduction.

Our analysis supports the safety of CR, because additional PCI did not increase the risk of complications, such as major bleeding, stroke, or contrast-induced acute kidney injury, compared with culprit-only PCI. However, there were a limited number of trials investigating such safety end points; thus, a definitive conclusion could not be drawn. Additional research should investigate such safety outcomes.

Several limitations apply to our analysis. First, as a meta-analysis, each trial's inclusion and exclusion criteria should be individually considered when extrapolating our results into practice. Patients with high-risk features, including cardiogenic shock and left main coronary artery disease, were excluded from the trials included in our study. Second, the cut-off for a significant lesion (FFR or angiographically) was variable in all trials. Third, only 1 study (FLOWER-MI) directly compared angiography- to an FFR-

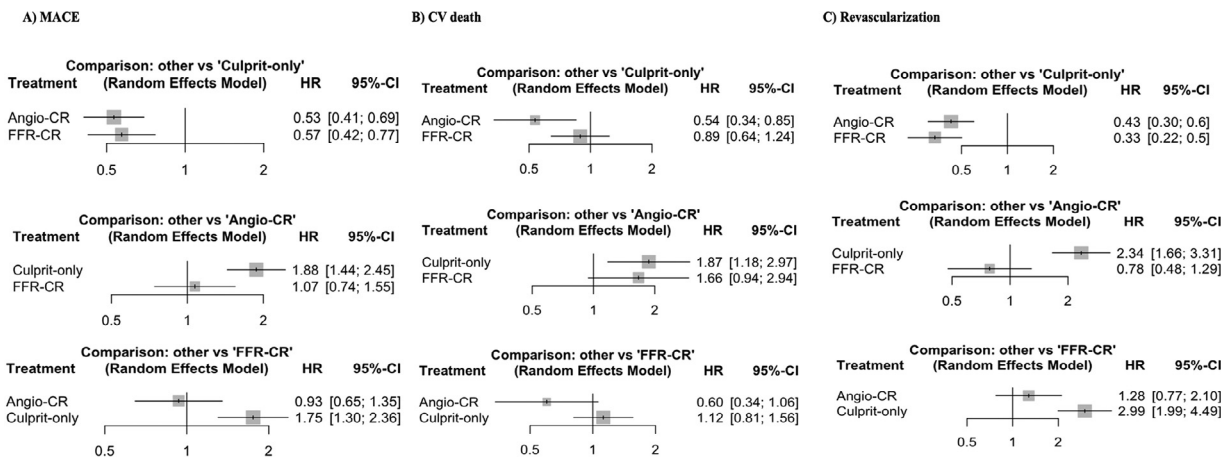

Figure 4. Results of Network meta-analysis for the outcomes of MACE, cardiovascular death, and revascularization. Forest plot for the comparisons among each treatment arm. Abbreviations as Figure 3.

guided CR approach; however, there was no inconsistency between direct and indirect comparisons. Fourth, many studies used a different definition of MACE, leading to moderate heterogeneity (I^2 = 54.2) for this outcome. Fifth, the positive signal seen with angiography-guided CR regarding CV death must be interpreted in the background of discrepancies in the trial data because 4 RCTs did not report the outcome.[9,14,17,18] Finally, there was variation in follow-up duration and in the timing of nonculprit vessel PCI between the studies included in this analysis.

Our meta-analysis suggests that in patients with MVD presenting with STEMI, CR had no significant benefit with an FFR-guided strategy compared with an angiography-guided strategy. Angiography-guided CR is associated with a lower incidence of all-cause death and MI in this population compared to culprit-only revascularization. Further large RCTs directly comparing patients who underwent angiography-guided PCI with FFR-guided PCI are warranted to draw a definitive conclusion.

Disclosures

Dr. Dangas reports receiving research grants to institution from Abbott, Medtronic, Boston Scientific, and Biotronik. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.08.005.

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