Meta-Analysis of Optimal Revascularization Strategy for Patients With ST-Segment Elevation Myocardial Infarction and Multi-Vessel Coronary Artery Disease

Rahman Shah, MD[a,b,*], Mannu Nayyar, MD[c], Francis K. Le, MD[a,b], Ajay Labroo, MD[a,b], Donnie A. Davis, MD[a,b], Emmanouil S. Brilakis, MD[d], and David E. Kandzari, MD[e]

Several clinical trials have shown that complete revascularization (CR) lowers the risks of revascularization and nonfatal myocardial infarction (MI) in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease compared with infarct-related artery-only revascularization (IRA-OR). However, individual trials have been underpowered for hard outcomes such as cardiovascular (CV) mortality. Therefore, we conducted an updated meta-analysis representing the largest sample size to date inclusive of contemporary studies comparing CR versus IRA-OR. Pooled risk ratios (RRs) were calculated using random effects model. Data from 11 RCTs involving 7,343 patients showed that compared with IRA-OR, CR was associated with lower CV mortality (RR 0.75; 95% confidence interval [CI] 0.57 to 0.99; p = 0.04), MI (RR 0.70; 95% CI 0.53 to 0.93), and recurrent revascularization (RR 0.38; 95% CI 0.27 to 0.54), but similar all-cause mortality (RR 0.85; 95% CI 0.70 to 1.05). In conclusion, in patients with STEMI and multivessel coronary artery disease, compared with IRA-OR, CR was associated with lower risk for CV mortality, MI, and recurrent revascularization, suggesting that CR should be the standard of care for STEMI patients. **(Am J Cardiol 2020;129:19−24)**

Primary percutaneous coronary intervention (PCI) of the culprit lesion is a standard of care for patients with ST-segment elevation myocardial infarction (STEMI), given its impact on survival.[1] However, approximately half of those patients have significant stenoses in noninfarct-related coronary arteries.[2] Historically, based on observational studies, PCI in a noninfarct-related artery at the time of primary PCI was considered harmful.[1] More recently, in patients with acute coronary stenoses, any residual stenosis after revascularization may represent a nidus for new events and is thus associated with poor prognoses at both 30 days and 1 year.[3] Over the last decade, evidence based on randomized clinical trials (RCTs) has emerged, revealing that complete revascularization (CR) decreases major adverse cardiac events (MACEs) compared with infarct-related artery-only revascularization (IRA-OR) in patients with STEMI.[4−13] However, in those trials, lower MACE rates were driven predominantly by lower risks of revascularization; individual trials were underpowered for hard outcomes such as cardiovascular (CV) mortality.[14,15] Therefore, we conducted an updated meta-analysis representing the largest sample size to date inclusive of contemporary studies comparing CR versus IRA-OR to compare clinical outcomes of myocardial infarction, repeat revascularization and cardiovascular mortality

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses.[16] Computerized literature searches of the PubMed, Google Scholar, and Cochrane databases were conducted to locate relevant RCTs. Searches were performed using various combinations of the following "infarct-related artery," "culprit," "revascularization," "ST-elevation myocardial infarction," "STEMI," "multivessel," "complete," "staged," "percutaneous coronary intervention," and "randomized controlled trial." In addition, abstracts from major international cardiology meetings were reviewed.

RCTs were included if subjects with acute STEMI and multivessel coronary artery disease (MV-CAD) who underwent primary PCI were enrolled and randomly assigned to either CR or IRA-OR. If one or more publications reported the same study, data for the longer term outcome was used.[6,17] Two investigators independently extracted data for study characteristics, design, outcomes, and funding sources. Any disagreements were resolved by consensus. The primary efficacy end point was CV mortality. The secondary efficacy end points were myocardial infarction (MI), revascularization, and all-cause mortality.

A standard pairwise meta-analysis was performed according to the Comprehensive Meta-Analysis system, version 3 (Comprehensive Meta-Analysis; Biostat Inc., Englewood, NJ). Pooled risk ratios (RRs) were calculated using random-effects models because this is the most

[a]Alabama College of Osteopathic Medicine, Dothan, Alabama; [b]Gulf Coast Medical center, Panama City, Florida; [c]University of Tennessee, Memphis, Tennessee; [d]Minneapolis Heart Institute, Minneapolis, Minnesota; and [e]Piedmont Heart Institute, Atlanta, Georgia. Manuscript received March 12, 2020; revised manuscript received and accepted May 12, 2020.

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*Corresponding author: Tel: (850) 872-3939; fax: (850) 872-3938.

E-mail address: shahcardiology@yahoo.com (R. Shah).

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conservative methodology to account for between-trial heterogeneity. Heterogeneity across trials was evaluated using the Cochran Q test and the Higgins I^2 test.[18] When heterogeneity was discovered, a sensitivity analysis was performed by excluding one study at a time and evaluating the impact on summary results.[19] An additional sensitivity analysis (for the primary end point) was performed excluding those 3 trials in which quality could not be assessed based on Cochrane Collaboration guidelines: one had not been published, and other two were published in non-English languages.[10,11,13]

Results

Eleven RCTs met the criteria for inclusion; these studies included 7,343 patients.[4–13,15] The search flow diagram is shown in eFigure S1 (Online Supplementary Appendix), and the bias assessment for each RCT is shown in eFigure S2 (Online Supplementary Appendix). Online eTable S1 (Online Supplementary Appendix) shows the inclusion and exclusion criteria for each trial.

Table 1 describes the characteristics of the individual trials. Most were multicentered but small to moderate in size, the exception being the COMPLETE trial.[15] The majority of the patient populations were male. In 3 trials (CvLPRIT [Complete versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease], COMPARE ACUTE [Comparison Between FFR Guided Revascularization versus Conventional Strategy in Acute STEMI Patients with MVD], and the one by Politi et al), intervention for nonculprit lesions was performed either during primary PCI or as a staged procedure at the discretion of the operator.[5,8] In 2 trials (HELP-AMI [HEpacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction] and PRAMI [Preventive Angioplasty in Acute Myocardial Infarction]), intervention for all nonculprit lesions were performed at the time of primary PCI.[4,7] In the remaining trials, nonculprit lesion interventions were performed as staged procedures either during the index hospitalization or later as an outpatient (Table 1). The decision to intervene for nonculprit lesions was based exclusively on fractional flow reserve (FFR) findings in the COMPARE ACUTE trial.[12] Three trials (DANAMI-3-PRIMULTI [Third Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction—Primary PCI in Multivessel], the one by Ghani et al, and COMPLETE) used both FFR and angiographic data to define the significance of the nonculprit lesion.[6,9,15] In the first 2, FFR was performed for the lesion with 50% to 90% stenosis; in the final, for that with 50% to 70% stenosis.[15] In the remaining trials, the decision to intervene for the nonculprit vessel was based solely on angiographic findings (Table 1). Follow-up duration ranged from 12 to 38 months.

Table 1
Baseline characteristics of included trials

Trial	Year	Study type	Patients (n)		Male (%)		DM (%)		Follow-up duration (months)	Definition of nonculprit lesion significance	Timing of nonculprit Lesion PCI	Staged PCI timing (days post-PPCI)
			IRA	CR	IRA	CR	IRA	CR				
HELP-AMI	2004	MC	17	52	85	88	41	12	12	n/a	IP	n/a
Politi et al	2010	SC	84	130*	76	78*	24	16*	30	>70% stenosis	IP & SP	56.8 ± 12.9†
Ghani et al	2012	SC	41	80	81	80	5.0	6.3	36	≥50% stenosis#	SP	7.5 (5-20)‡
PRAMI	2013	MC	231	234	81	76	21	15	23	≥50% stenosis	IP	n/a
CvLPRIT	2014	MC	146	150	77	85	14	13	12	>70% stenosis	IP & SP	Index Hosp
Estevez-Loureir et al	2014	n/a	99	100	n/a	n/a	n/a	n/a	12	n/a	n/a	n/a
Zhang et al	2015	n/a	213	215	n/a	n/a	n/a	n/a	24	n/a	n/a	7-10§
DANAMI-3-PRIMULTI	2015	MC	313	314	81	80	13	9	27	>50% stenosis#	SP	2
PRAGUE-13	2015	MC	108	106	n/a	n/a	n/a	n/a	38	≥70% stenosis	n/a	3-40§
COMPARE ACUTE	2017	MC	590	295	76	79	16	15	12	>50% stenosis of ≥#	IP &SP	SP: 2.1 ± 1
COMPLETE	2019	MC	2025	2016	79	81	20	19	36	>70% stenosis#	IP & SP	SP: 23.0 (12.5-33.5)‡

CA = coronary artery, COMPARE ACUTE = Comparison Between FFR Guided Revascularization versus Conventional Strategy in Acute STEMI Patients with MVD, COMPLETE = Complete Revascularization with Multivessel PCI for Myocardial Infarction, CR = complete revascularization, CvLPRIT = Complete versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease, DANAMI-3-PRIMULTI = third Danish study of optimal acute treatment of patients with ST-segment elevation myocardial infarction-primary PCI in multivessel disease, DM = diabetes mellitus, HELP-AMI = HEpacoat for culprit or multivessel stenting for acute myocardial infarction, IH = index-hospitalization, IP = index procedure, IRA = infarct-related artery only revascularization, MC = multicenter, n/a = not applicable, PPCI = primary percutaneous coronary intervention, PRAGUE-13 = Multivessel coronary artery disease diagnosed at the time of primary PCI for STEMI, PRAMI = Preventive Angioplasty in Myocardial Infarction, SC = single center, SP = staged procedure.

* Includes staged revascularization, weighted average.

Includes use of fractional flow reserve prior to PCI of nonculprit vessel.

Ghani—PCI to any vessel with FFR <0.75 or >90% stenosis.

DANAMI-3-PRIMULTI—PCI to any vessel with FFR ≤0.80 or >90% stenosis.

COMPARE ACUTE—PCI to any vessel with FFR ≤0.80.

COMPLETE—PCI to any vessel with FFR ≤0.80 or >70% stenosis.

† Mean.

‡ Median (interquartile range)

§ Range.

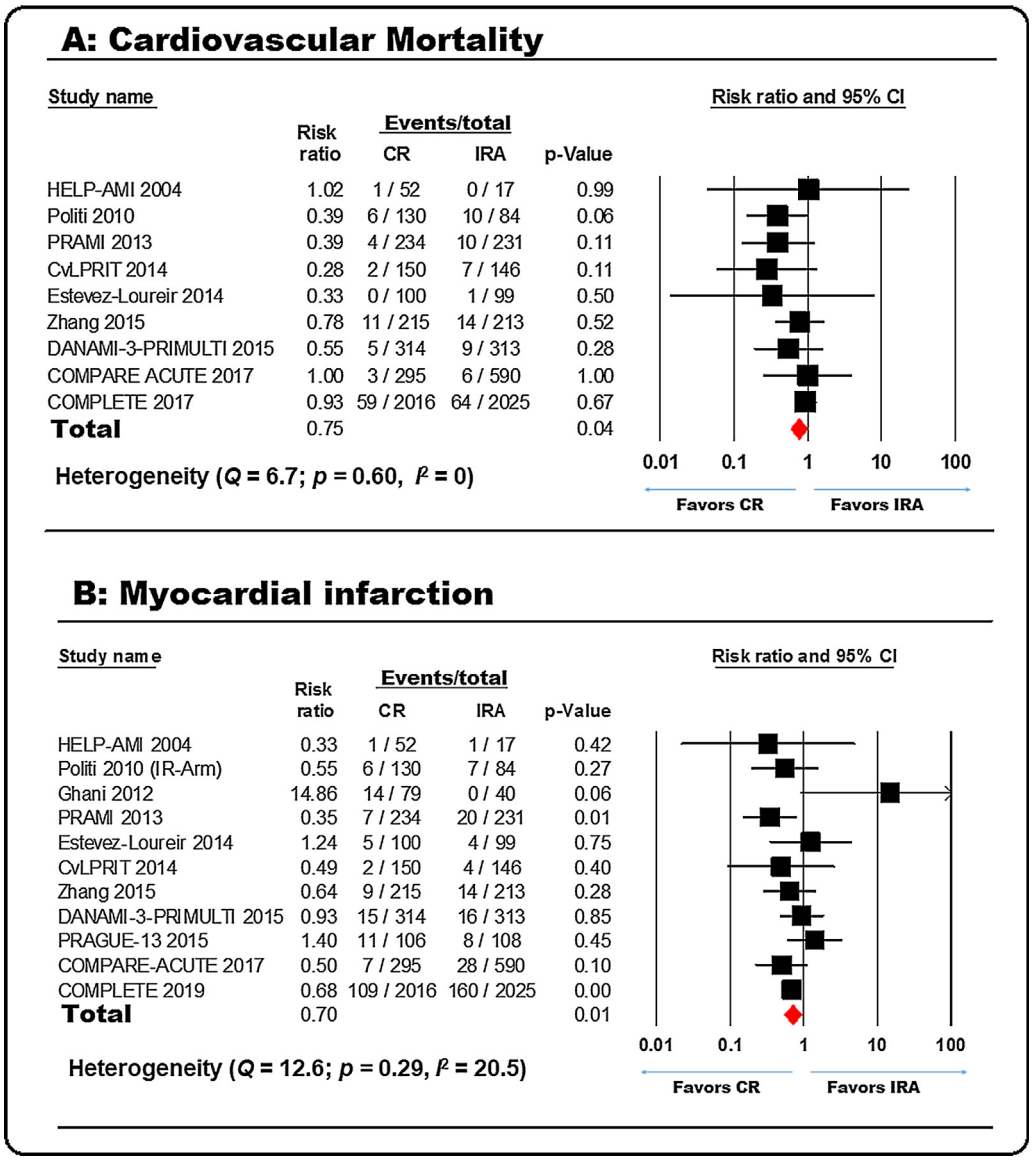

Figure 1. Individual and pooled risk ratios for *(A)* cardiovascular mortality and *(B)* myocardial infarction. CI = confidence interval; CR = complete revascularization; IRA = infarct-related artery-only revascularization.

The angiographic findings of the included trials are shown in Table S2 (Online Supplementary Appendix). The majority of the patients were diagnosed with 2-vessel CAD, and 3-vesssel CAD was present in about one third. The right coronary artery was the most frequent culprit artery in the majority of the trials. In contrast, the left anterior descending artery was the most common nonculprit artery; it was the culprit artery in about one-third of all patients.

CR decreased the risk of CV mortality by 25% (RR 0.75; 95% confidence interval [CI] 0.57 to 0.99; p = 0.04) compared with IRA-OR (Figure 1). Significant heterogeneity was not found for CV mortality between the trials. The sensitivity analysis (exclusion of the 3 low-quality trials) showed that the pooled estimate remained significant, favoring the CR group (eFigure S3 in the Supplementary Appendix).

CR also decreased the risk of recurrent MI by 30% (RR 0.70; 95% CI 0.53 to 0.93; p = 0.01) compared with IRA-OR (Figure 1). Again, no significant heterogeneity was found between the trials. Similarly, the risk for the recurrent revascularization was lower with CR (RR 0.34; 95% CI 0.27 to 0.54; p <0.001) compared with IRA-OR (Figure 2). However, mild heterogeneity was found between the trials for this outcome. Sensitivity analysis showed that the removal of any single study did not affect summary results (eFigure S4 in the Supplementary Appendix).

Finally, no statistically significant difference was found between the two revascularization strategies for the risk of total mortality (RR 0.85; 95% CI 0.70 to 1.05), though all-cause mortality was numerically lower with CR compared with IRA-OR (165 events per 3,691 patients vs 189 events

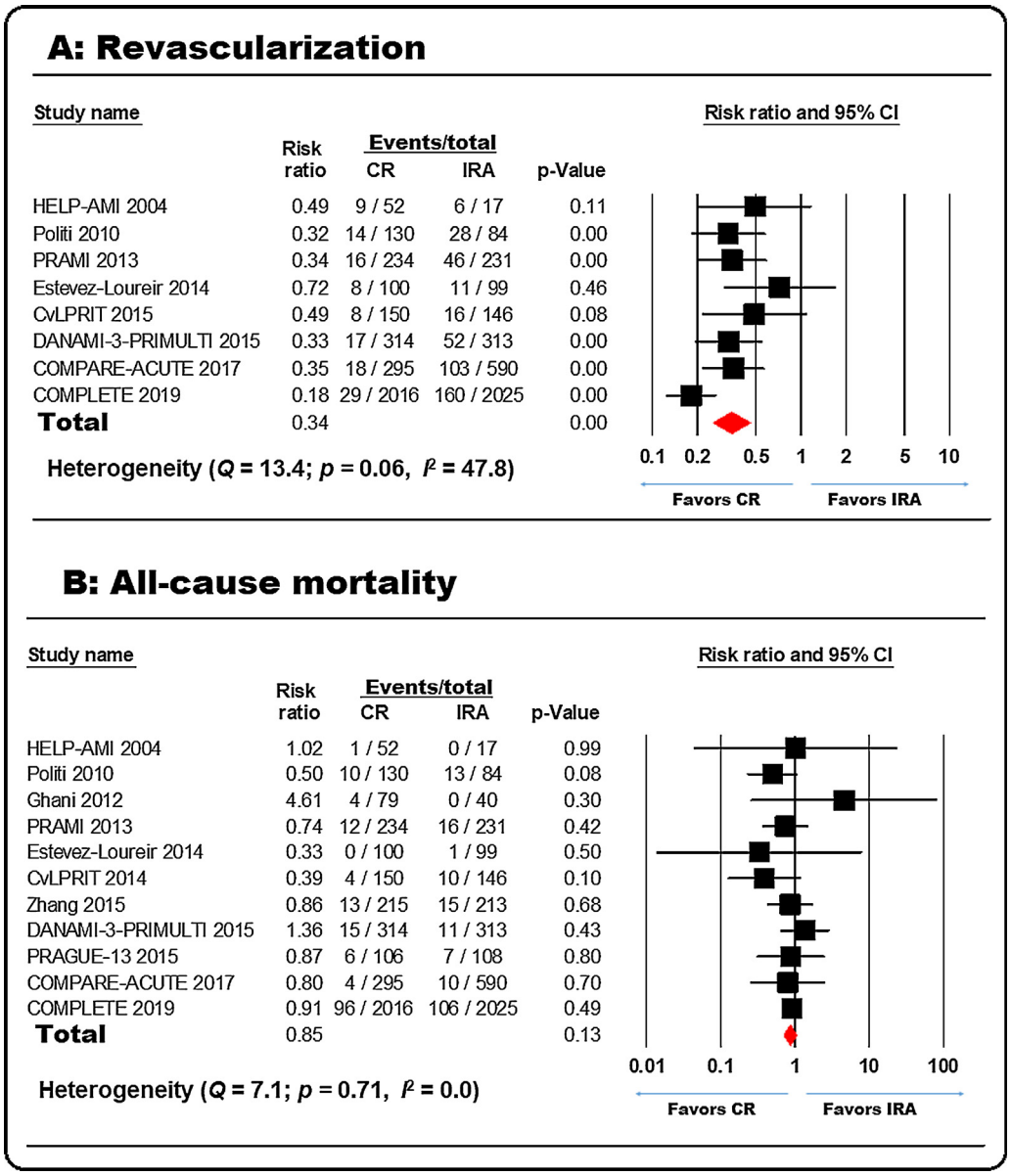

Figure 2. Individual and pooled risk ratios for *(A)* revascularization and *(B)* all-cause mortality. CI = confidence interval; CR = complete revascularization; IRA = infarct-related artery-only revascularization.

in 3,866 patients). No significant heterogeneity was found between the trials for all-cause mortality.

Discussion

This updated meta-analysis of eleven RCTs involved the largest number (n = 7,343) of patients ever reported. These data show that in patients with STEMI and MV-CAD, CR decreased the risk of CV mortality by 25% and MI by 30% compared with IRA-OR. Furthermore, it was associated with a 66% lower risk of recurrent revascularization. These findings support existing European guidelines (Class IIa), which recommend that CR should be considered for patients with STEMI and MV-CAD before hospital discharge.[20] They also inform American guidelines to advance the current Class IIB recommendation to perform CR in patients with STEMI and MV-CAD.[14]

Primary PCI of the culprit lesion is the preferred reperfusion strategy in patients with STEMI.[1] However, half of these patients also have MV-CAD, the combination presenting a setting associated with poor outcomes compared with single-vessel disease.[2] Historically, guidelines have discouraged CR during primary PCI because of associated risk described in observational studies.[1,14] However, in the last decade, several RCTs have suggested that CR improves outcomes compared with IRA-OR. Similarly, several meta-analyses have shown that CR decreases the MACE rate and that this is predominantly driven by a lower rate of revascularization.[21–25] However, since those meta-analyses, new RCTs, including the COMPLETE trial—the largest RCT examining revascularization strategies in STEMI, enrolling

more patients individually than the previous ten trials combined—have been reported, rendering previous meta-analyses arguably outdated.[21–23] Furthermore, by including this trial, we were able to show that CR not only improves outcomes such as revascularization but also hard end points such as CV death. Even a trial as large as the COMPLETE trial can be underpowered for showing a significant difference in individual outcomes (such as CV mortality) because the sample size was calculated based on a composite end point.

The poor prognoses for patients with STEMI and MV-CAD are likely multifactorial. They include diffuse atherosclerosis with larger ischemic burdens, multiple stenoses with impaired contractility of noninfarct zones, multiple unstable plaques with recurrent ACS, and adverse left ventricular remodeling due to poor perfusion to watershed areas (even after restoring flow to the culprit area) from the flow-limiting stenoses in adjacent nonculprit arteries.[26,27] Historically, the better outcomes with CR compared with IRA-OR were thought to result from preventing infarct extension and adverse remodeling through increases in myocardial salvage and blood flow to the watershed areas.[26–28] However, in a cardiac magnetic resonance substudy of the DANAMI-3-PRIMULTI, CR did not affect final infarct size, left ventricular function, or remodeling compared with IRA-OR at 3 months follow-up.[29] In addition, in the COMPLETE trial, consistent benefits of CR were observed regardless of the point at which nonculprit-lesion intervention was performed (during the index hospitalization or several weeks [median, 23 days] after discharge).[15] In this trial, most of the benefits of CR seemed to have occurred more than 45 days after intervention, and Kaplan-Meier curves showed continued divergence over time. Similarly, in a broad spectrum of patients with CAD, multiple studies have shown that CR compared with incomplete revascularization improved not only soft outcomes (i.e., recurrent revascularization), but also hard outcomes such as MI and mortality.[30] These findings suggest that the benefit of CR in patients with STEMI and MV-CAD is the result of decreases in total ischemic burden.

This meta-analysis has several limitations. First, the timing of intervention to nonculprit lesions varied across trials. Although current European guidelines recommend that PCI on nonculprit lesions be performed before hospital discharge, they were published before the results of the COMPLETE trial were available.[20] The COMPLETE investigators showed that PCI on nonculprit lesions can be safe and efficacious even when performed as late as 23 days after the index event.[15] Second, the diagnostic test to define a significant obstructive lesion in the nonculprit vessel varied across studies: some used angiographic data only, and others used functional studies such as FFR. In the past, the accuracy of FFR in a setting of ACS, even for nonculprit lesions, has been of concern. However, recent strong scientific evidence shows that FFR is accurate for the functional assessment of nonculprit lesions during STEMI.[12] Therefore, using FFR measurements seems acceptable during acute MI whether or not the nonculprit lesion is functionally significant.

In conclusion, in patients with STEMI and multivessel disease, CR compared with IRA-OR decreases the risks of CV mortality, MI, and recurrent revascularization. Therefore, in patients with STEMI and MV-CAD, CR should be the standard of care. This meta-analysis of RCTs also suggests that current American guidelines should be updated.

CRediT Author Statement

Author Contributions: Dr Shah had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Shah, Nayyar, Le, Davis, Labroo

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Shah

Critical revision of the manuscript for important intellectual content: Kandzari, Brilakis

Statistical analysis: Shah, Nayyar, Le, Davis, Labroo

Administrative, technical, or material support: Nayyar, Le, Davis, Labroo

Supervision: Kandzari, Brilakis,

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.05.016.

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