Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials for Multivessel PCI Versus Culprit Artery Only PCI in STEMI Without Cardiogenic Shock

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Abstract: ***Background:*** **Traditionally ST-elevation myocardial infarction (STEMI) with multivessel coronary artery disease is treated with percutaneous coronary intervention (PCI) to culprit lesion only. The benefit of multivessel (MV) PCI among STEMI patients without cardiogenic shock is unclear.** ***Methods:*** **PubMed, EMBASE, and Cochrane Database were searched from 1996 to 2019, for studies of patients with STEMI without cardiogenic shock, who underwent PCI. Only randomized controlled trials comparing culprit PCI to MV PCI vs culprit vessel PCI were included for pairwise meta-analysis. All-cause mortality, cardiac mortality, reinfarction, revascularization and major adverse cardiovascular events (MACE) were compared. Trial sequential analysis (TSA) was performed for outcome variables.** ***Results:*** **Nine randomized controlled trials contributed 6930 patients meeting inclusion criteria. Three thousand three hundred seventy-six underwent MV PCI, and 3554**

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underwent culprit PCI. Our analysis demonstrated no significant difference in all-cause mortality. MV PCI had a lower risk of cardiac mortality, reinfarction, MACE and repeat revascularization compared to culprit PCI (*P* values <0.05). TSA showed futility for further trials to detect all-cause mortality benefit and lack of firm evidence of benefit in cardiac mortality and re-infarction, but firm evidence of benefit in revascularization and MACE. *Conclusions:* In conclusion, MV PCI strategy was beneficial in reducing cardiac mortality, reinfarction, repeat revascularization, and MACE but there was no all-cause mortality benefit when compared to culprit only PCI strategy. Evidence for benefit in cardiac mortality and re-infarction is not robust per TSA. (Curr Probl Cardiol 2021;46:100646.)

Introduction

Multivessel coronary artery disease (CAD) is seen in about 40% of patients with ST-elevation myocardial infarction (STEMI).[1] Multivessel disease in STEMI is associated with higher morbidity and mortality compared to single-vessel CAD.[2] About 6%-12% of patients presenting with STEMI may present with cardiogenic shock.[3–5] Multiple studies have shown the benefit of emergent revascularization of the culprit vessel in improving mortality in patients with multivessel CAD presenting with STEMI and cardiogenic shock.[6,7] However, the majority of the patients with STEMI do not have a cardiogenic shock at the time of presentation. Studies comparing multivessel PCI with culprit artery only PCI in patients without cardiogenic shock are inconsistent in their findings.

The guidelines regarding the management of STEMI patients without cardiogenic shock have changed over the last decade. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines advised against PCI of the nonculprit artery (Class IIIB).[8] However, the focused update in 2015 recommended considering PCI of the nonculprit artery as well in stable patients (Class IIB).[9] The 2014 European Society of Cardiology (ESC) guidelines advised considering PCI of nonculprit artery on a case by case basis (Class IC).[10] However, the 2018 update recommended considering fractional flow reserve guided PCI for the nonculprit artery (Class IIA).[11] The old recommendations were based on multiple observational studies, registry data, and one meta-analysis

showing increased major adverse cardiovascular events (MACE) and in-hospital mortality in the case of multivessel PCI.[3−5,12]

A study by Wald et al on multivessel PCI, which included noninfarct artery PCI of vessels with major stenosis when compared to culprit only PCI, found that multivessel PCI reduced the risk of adverse cardiovascular events without any mortality benefit.[13] A recently published meta-analysis incorporating several RCTs showed that multivessel PCI strategy was beneficial in reducing cardiac mortality and need for repeat revascularization; however there was no benefit in all-cause mortality and myocardial infarction.[14] Even the Culprit Lesion Only PCI vs Multivessel PCI in Cardiogenic Shock trial showed patients who underwent culprit artery PCI to have lower mortality and severe renal failure.[15]

The Complete vs Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial included 4041 patients and found conflicting results in terms of cardiac mortality, myocardial infarction, and revascularization.[15] It showed a reduction in reinfarction and repeat revascularization when comparing multivessel PCI to culprit only PCI but did not find a significant difference in all-cause or cardiovascular mortality between the 2 groups.

In view of conflicting results of past observational studies, previous RCTs, meta-analysis, and results of the more recent COMPLETE trial, we performed a systematic review, meta-analysis and trial sequential analysis of all the available published RCTs to compare all-cause mortality and cardiac mortality among patients undergoing multivessel PCI vs culprit only PCI in STEMI patients without cardiogenic shock. We also studied other outcomes, including reinfarction, repeat revascularization, and MACE. The risk of bias analysis was performed for individual RCT to ascertain the quality of individual studies.

Methods

We performed a systematic review in accordance with the Cochrane Handbook for Systematic Reviews and Intervention. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement in health care interventions.[16,17]

Search Strategy

We systematically searched PubMed, EMBASE, Google Scholar, Cochrane Central Register of Controlled Trials, and Scopus databases from October 1996 to October 31, 2019. Following keywords:

"myocardial infarction," "percutaneous coronary intervention," "coronary angioplasty," "ST-elevation myocardial infarction," "STEMI," "culprit," "multivessel," "nonculprit," "culprit percutaneous coronary intervention," "culprit-PCI," "multivessel percutaneous coronary intervention," "multi-vessel PCI," "complete revascularization," "staged percutaneous coronary intervention," "randomized controlled trial," and "RCT" were used. We also reviewed references of the selected studies, conference abstracts, systematic reviews until we started getting duplicate results. There was no language restriction for the search.

Study Selection

Two reviewers (M.W.T. and D.R.) independently reviewed all the titles and abstracts for inclusion criteria as follows: Studies with myocardial infarction, RCT comparing culprit only PCI vs complete or staged PCI and studies with outcome data for all-cause mortality, cardiac mortality, reinfarction, revascularization, and MACE were available. Studies comparing alternate revascularization or surgeries were excluded. Study population with cardiogenic shock or hemodynamic instability were excluded. Unpublished citations were included to address negative publication bias. The quality of abstracted studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias for randomized studies. Trials were categorized as high, low or unclear risk of bias. Data were extracted from included studies by 2 reviewers independently (M.W.T. and D.R.). In case of conflict regarding the inclusion of studies and its characteristics, a consensus was achieved through discussion with a senior author (B. B.).

Statistical Analysis

The meta-analysis was performed with the recommendation from Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16,18] All statistical analyses were performed using Review Manager 5.[19] Risk Ratios (RR) with 95% confidence intervals (CI) were used as summary estimated. Mantel-Haenszel fixed-effects or random-effects models (where appropriate) were used to calculate pooled RR. Heterogeneity was measured with I^2 index. An I^2 of less than 40% was deemed as low heterogeneity, between 40% and 60% as moderate, and over 60% as high heterogeneity.[20] Leave-one-out sensitivity analysis was performed where necessary to identify studies contributing to the heterogeneity of significance.

Trial Sequential Analysis

Cumulative meta-analyses are prone to producing spurious significant *P* values. This occurs due to repeated testing of significance as trial data accumulates over the years. Information size (cumulative sample size) in a meta-analysis should match that of an adequately powered trial. Trial sequential analysis (TSA) solves this problem by performing sequential analyses analogous to interim analyses of a single trial performed to detect whether significance for anticipated effect or futility is reached and if the trial could be terminated early.

TSA was performed using TSA software version 0.9 Beta.[21] All analyses were performed with 2-way testing, α of 5%, power $(1 - \beta)$ of 80%, relative risk reduction of 25% for calculating information size after adjusting for diversity. This methodology has been previously described.[22,23] The 25% relative risk reduction was chosen as it is clinically meaningful and realistic as seen in other cardiovascular trials. The software generates graphics for individual outcomes, plotting the cumulative trial data along with both conventional boundaries as well as TSA boundaries for effect and futility.

Results

Search and Study Selection

Our search yielded 1099 studies. Another 17 additional records were identified through other sources. After eliminating duplicates, 985 studies were identified. Approximately, 880 studies were rejected due to poor relevance after titles and abstracts review. The remaining studies were reviewed and assessed for eligibility based on the inclusion and exclusion criteria, yielding 9 studies that met the predetermined criteria for this analysis (Fig 1).[4,13,15,24–30]

Baseline Characteristics

The pooled data provided a total of 6930 patients undergoing PCI, with 3376 patients in the multivessel PCI group and 3554 patients in the culprit only PCI group. Table 1 summarizes the characteristics of the 9 studies included in this meta-analysis. Online Table 2 shows the respective outcomes studied in individual RCTs, and patients' baseline characteristics are listed in online Table 3.

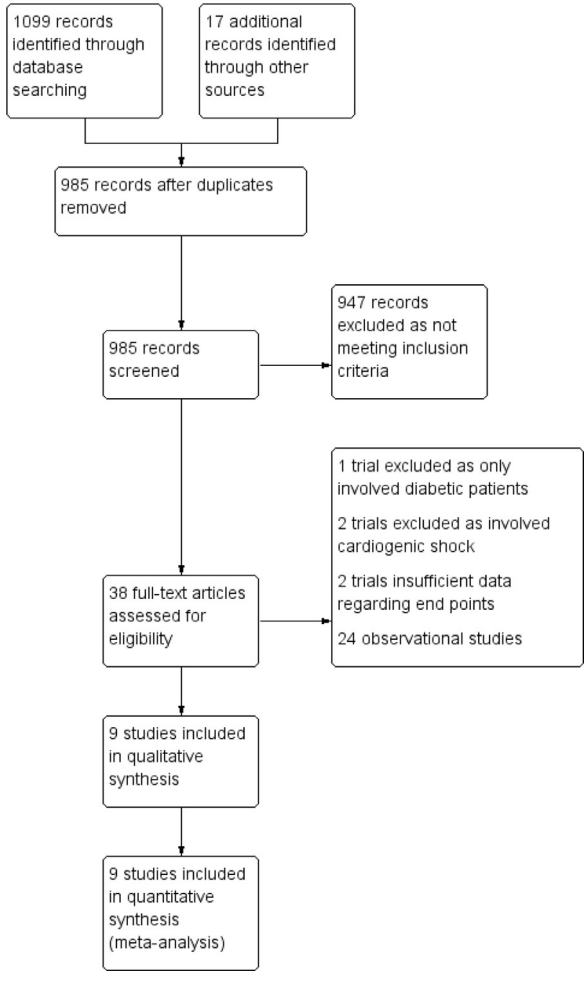

FIG 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart illustrating the search strategy.

Primary Outcomes

Primary outcomes included all-cause mortality and cardiac mortality. Figure 2 shows forest plots for both components of the primary outcome. In the pooled population, 152 patients (4.5%) treated with multivessel PCI and 173 patients (4.8%) treated with culprit only PCI did not survive during the 12-38-month follow-up period (risk ratio [RR] 0.86, 95% confidence interval [CI] 0.70-1.07, $P = 0.18$). The cardiac mortality analysis revealed 81 (2.5%) deaths in the multivessel PCI group and 106 (3.1%)

TABLE 1. Study characteristics

Study	Design	Number of patients			Inclusion criteria	Exclusion criteria	Follow up (months)
		CO PCI	MV PCI				
			Index	Staged			
Di Mario et al, 2004 (28)	Prospective, randomized, multicenter study	17	52	-	▪ Ischemic chest pain < 12 h. ▪ ST-segment elevation of ≥ 1 mm in 2 or more contiguous electrocardiographic leads or 2 mm in the precordial leads.	▪ Significant lesions in vein grafts or arterial conduits or in segments previously treated with angioplasty or stent implantation. ▪ Recent thrombolysis (less than 1 wk). ▪ Cardiogenic shock. ▪ Single vessel disease. ▪ Left main stenosis of 50%. ▪ Intention to treat > 1 totally occluded major epicardial vessel. ▪ Diffuse calcification. ▪ Severe tortuosity in the culprit and nonculprit arteries.	12
Politi et al, 2010 (25)	Prospective, randomized study	84	65	65	▪ Chest pain >30 min and < 12 h. ▪ STEMI per AHA/ ACC guidelines.	▪ Cardiogenic shock. ▪ Left main disease. ▪ Previous CABG. ▪ Severe valvular disease. ▪ Unsuccessful procedures.	30
Ghani et al, 2012 (26)	Prospective, randomized study	40	79	-	▪ Patients who had successful PCI; defined as a residual diameter stenosis of $< 50\%$ and TIMI ≥ 2 flow. ▪ Multivessel disease was defined as ≥ 1 stenosis and ≥ 2 major epicardial coronary arteries, or the combination of a side branch and a main epicardial vessel provided that they supply different territories.	▪ An urgent indication for additional revascularization. ▪ 80 years old. ▪ Chronic occlusion of one of the noninfarct-related arteries. ▪ Prior CABG. ▪ Left main stenosis of $\geq 50\%$, re-stenotic lesions in noninfarcted arteries.	36

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TABLE 1. (*continued*)

Study	Design	Number of patients			Inclusion criteria	Exclusion criteria	Follow up (months)
		CO PCI	MV PCI				
			Index	Staged			
					▪ A significant stenosis was defined as a diameter stenosis of $\geq$ 50% in luminal diameter. The minimal luminal diameter adjacent to the lesion to be treated had to be $\geq$ 2.5 mm.	▪ Chronic atrial fibrillation. ▪ Limited life expectancy. ▪ Factors that made complete follow-up unlikely.	
Wald et al, 2013 (13)	Prospective, randomized, multicenter study	231	234	-	▪ STEMI AHA/ACC guidelines. ▪ Successfully treated artery and $\geq$ 1 noninfarct related artery with $\geq$ 50% stenosis that are amenable to PCI treatment.	▪ Cardiogenic shock. ▪ Left main disease or equivalent. ▪ Previous CABG. ▪ Unable to provide consent. ▪ Chronic total occlusion.	23
Gershlick et al, 2015 (30)	Open label, prospective, randomized, multicenter study	146	150	-	▪ Chest pain less than 12 h. ▪ Suspected or proven STEMI. ▪ Infarct related artery plus $\geq$ 1 noninfarct-related epicardial artery $>$ 2 mm with $\geq$ 1 lesion $>$ 70% diameter stenosis in one plane or $>$ 50% in 2 planes.	▪ Previous Q wave myocardial infarction. ▪ Previous CABG. ▪ Cardiogenic shock. ▪ VSD or moderate/severe mitral regurgitation. ▪ Chronic kidney disease (eGFR $<$ 30 mL/minute/1.73 m^2). ▪ Suspected or confirmed thrombosis of a previously stented artery. ▪ Chronic total occlusion.	12

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TABLE 1. (*continued*)

Study	Design	Number of patients			Inclusion criteria	Exclusion criteria	Follow up (months)
		CO PCI	MV PCI				
			Index	Staged			
Engstrom et al, 2015 (27)	Open lab, randomized, controlled trial	313	314	-	▪ Chest pain of less than 12 h ▪ ST segment elevation greater than 1 mm and at least 2 contiguous leads, ▪ Patients with angiographic diameter stenosis of greater than 50% in ≥ 1 noninfarct-related arteries.	▪ Intolerance of contrast media or of relevant anticoagulant or antithrombotic drugs. ▪ Unconsciousness. ▪ Cardiogenic shock. ▪ Stent thrombosis. ▪ Indication for CABG. ▪ Increased bleeding risk.	27
Hlinomaz et al, 2015 (29)	Open, prospective, randomized, multicenter trial	108	-	106	▪ STEMI after successful primary PCI to infarct related artery, and at least one stenosis of ≥ 70% of noninfarct related coronary arteries with diameter of ≥ 2.5-mm. ▪ Enrollment ≥ 48 h following onset of symptoms.	▪ Left main disease with ≥ 50% stenosis. ▪ Significant valvular disease. ▪ Cardiogenic shock. ▪ Hemodynamic instability. ▪ Angina pectoris > grade 2 CCS lasting 1 mo prior to STEMI.	38
Smits et al, 2017 (24)	Prospective, randomized, multicenter trial	590	295	-	▪ 18-85 y of age. ▪ STEMI within 12 h ▪ Noninfarct related coronary arteries (or their major side branches ≥ 2 mm in diameter) have ≥ 50% stenosis. ▪ Eligible for PCI.	▪ Left main disease. ▪ STEMI due to in-stent thrombosis. ▪ CTO of nonculprit vessel. ▪ Severe stenosis with TIMI flow < 2 of the nonculprit vessels. ▪ Complicated culprit patient treatment with one or more of the following: (1) extravasation, (2) permanent no reflow after culprit lesion treatment, and (3) inability to implant a stent. ▪ Severe valve dysfunction requiring surgery. ▪ Life expectancy < 2 y. ▪ Pregnancy or planning to become pregnant.	36

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TABLE 1. (*continued*)

Study	Design	Number of patients			Inclusion criteria	Exclusion criteria	Follow up (months)
		CO PCI	MV PCI				
			Index	Staged			
Mehta et al, 2019 (15)	Multinational, randomized trial	20252016	-		▪ STEMI after successful culprit lesion PCI. ▪ Multi-vessel coronary artery disease defined as of the presence of $\geq$ 1 angiographically significant noninfarct related lesion, and was located in a vessel with a diameter of $\geq$ 2.5 mm. ▪ Nonculprit lesions were deemed angiographically significant if they were associated with at least 70% stenosis of the vessel diameter on visual estimation or with 50%-69% stenosis accompanied by fractional flow reserve measurement of 0.80 or less.	▪ An intention before randomization to revascularize a nonculprit lesion. ▪ A planned surgical revascularization. ▪ Previous CABG. ▪ Noncardiovascular comorbidity reducing life expectancy to less than 5 y. ▪ Expected limited $<$ 5-year follow-up.	36

ACC/AHA, American college of cardiology, American Heart Association; CO, culprit only; MV, multiple vessel; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

TABLE 2. Study outcomes

Study	Primary outcome	Secondary outcome
Di Mario et al, 2004	Repeat revascularization over 12 mo.	Incidence of adverse in-hospital events, safety of the multivessel treatment strategy in acute MI, procedural cost in-hospital and at 12-months.
Politi et al, 2010	MACE defined as cardiac or noncardiac death, in-hospital death, reinfarction, rehospitalization for acute coronary syndrome, and repeat coronary revascularization.	-
Ghani et al, 2012	Ejection fraction at 6 mo.	Major Adverse Cardiac Events (MACE) after 3 y of follow-up. MACE included death, nonfatal reinfarction, and additional revascularization procedures.
Wald et al, 2013	Composite of death from cardiac causes, nonfatal MI, or refractory angina.	Death from noncardiac causes, and repeat revascularization
Gershlick et al, 2015	MACE defined as all-cause mortality, recurrent MI, heart failure hospital admission, and repeat revascularization.	-
Engstrom et al, 2015	A composite of all-cause mortality, reinfarction, or ischemia driven revascularization of lesions in noninfarct-related coronary arteries.	Components of the primary endpoint, occurrence of cardiac death, and urgent and nonurgent PCI of lesions in noninfarct related arteries.
Hlinomaz et al, 2015	All-cause mortality, nonfatal MI, and cerebrovascular accidents.	Hospitalization for unstable angina, revascularization of noninfarct-related coronary arteries, cardiovascular death, hospitalization for heart failure.
Smits et al, 2017	A composite of death from any cause, nonfatal MI, any revascularization, and cerebrovascular events at 12 mo.	The primary endpoint at 24 and 36 mo Composite of cardiac death, myocardial infarction, any revascularization, stroke, and major bleeding Composite of hospitalization for heart failure and unstable angina pectoris; Any revascularization Stent thrombosis Bleeding at 48 h and at 12 mo
Mehta et al, 2019	Composite of cardiovascular death or myocardial infarction. Composite of cardiovascular death, myocardial infarction, or ischemia driven revascularization.	Each component of the primary outcome All-cause mortality, unstable angina, new or worsening New York Heart Association class IV heart failure, stroke, and stent thrombosis

TABLE 3. Patient baseline characteristics

Study	Procedure	Mean Age years ± SD (Range)	Male sex *n* (%)	Diabetes *n* (%)	Hyper-tension, *n* (%)	Anterior Infarct, *n* (%)	Chronic renal insufficiency *n* (%)	Previous MI *n* (%)	Current smoker *n* (%)	Dyslipide-mia *n* (%)	Previous PCI *n* (%)	Previous stroke *n* (%)	Time from previous onset to index PCI *n* (%)			Killip class > 2 *n* (%)	Medications at discharge *n* (%)				
													<6 h	6-12 h	>12 h		Aspirin	P2Y12 inhibitor	Statin	Beta blockers	ACE inhibitor
Di Mario et al 2004	Multivessel *n* = 52	63.5 ± 12.4	46 (88.5)	21 (40.4)	30 (57.7)	27 (51.9)	-	-	34 (66.6)	21 (41.2)	-	-	-	-	-	10 (20)	-	-	-	-	-
	Culprit *n* = 17	65.3 ± 7.4	14 (82.4)	2 (11.8)	6 (35.3)	10 (58.8)	-	-	13 (81)	9 (52.9)	-	-	-	-	-	3 (18.8)	-	-	-	-	-
Gershlick et al, 25 2015	Multivessel *n* = 150	64.6 ± 11.2	128 (85.3)	19 (12.7)	54 (36.0)	54 (36.0)	1 (0.7)	7 (4.8)	50 (34.3)	41 (27.9)	6 (4.1)	-	-	-	-	10 (6.8)	-	-	-	-	-
	Culprit *n* = 146	65.3 ± 11.9	112 (76.7)	20 (13.7)	51 (34.9)	52 (35.6)	1 (0.7)	5 (3.6)	37 (26.8)	34 (24.3)	3 (2.1)	-	-	-	-	13 (9.4)	-	-	-	-	-
Complete trial (Mehta 2019)	Multivessel *n* = 1853	61.6 ± 10.7	1623 (80.5)	385 (19.1)	982 (48.7)	-	37 (2.0)	148 (7.3)	819 (40.6)	764 (37.9)	142 (7.0)	64 (3.2)	1383 (69.4)	322 (16.1)	289 (14.5)	212 (10.6)	2011 (99.8)	2003 (99.4)	1980 (98.2)	-	1723 (85.5)
	Culprit *n* = 1885	62.4 ± 10.7	1602 (79.1)	402 (19.9)	1027 (50.7)	-	44 (2.3)	154 (7.6)	787 (38.9)	797 (39.4)	141 (7.0)	62 (3.1)	1341 (67)	354 (17.7)	305 (15.2)	218 (10.9)	2015 (99.5)	2018 (99.7)	1968 (97.2)	-	1714 (84.6)
Politi et al 2010	MV index = 65	64.5 ± 11.7	50 (76.9)	9 (13.8)	32 (49,2)	31 (47.7)	17 (26.6)	-	-	-	5 (7.7)	-	-	-	-	-	62 (98.4)	61 (96.8)	57 (90.5)	52 (82.5)	35 (55.6)
	Culprit *n* = 84	66.5 ± 13,2	64 (76.2)	20 (23.8)	50 (59.5)	35 (41.7)	24 (29.3)	-	-	-	10 (11.9)	-	-	-	-	-	74 (96.1)	71 (92.2)	68 (88.3)	62 (80.5)	48 (62.3)
	MV staged =65	64.1 ± 11.1	52 (80)	12 (18.5)	42 (64.6)	28 (43.8)	16 (24.6)	-	-	-	6 (9.2)	-	-	-	-	-	65 (100)	65 (100)	60 (92.3)	52 (80)	38 (58.5)
Smiths (COMPARE-ACUTE) 2017	Multivessel *n* = 295	62 ± 10	233 (79)	43 (14.6)	136 (46.1)	105 (35.6)	3 (1.0)	22 (7.5)	120 (40.8)	95 (32.2)	25 (8.5)	10 (3.4)	225 (76.3)	47 (15.9)	23 (7.8)	15 (5.1)	-	-	-	-	-
	Culprit *n* = 590	61 ± 10	450 (76.3)	94 (15.9)	282 (47.8)	206 (34.9)	7 (1.2)	48 (8.1)	287 (589)	176 (29.8)	44 (7.5)	26 (4.4)	462 (78.3)	84 (14.2)	44 (7.5)	30 (5.1)	-	-	-	-	-
Wald (PRAMI) 2013	Multivessel *n* = 234	62 (32−92)	177 (76)	35 (15)	94 (40)	67 (29)	-	19 (8)	118 (50)	-	-	10 (4)	-	-	-	-	-	-	-	-	-
	Culprit *n* = 231	62 (33−90)	186 (81)	48 (21)	93 (40)	89 (39)	-	16 (7)	103 (45)	-	-	10 (4)	-	-	-	-	-	-	-	-	-

(*continued on next page*)

TABLE 3. (*continued*)

Study	Procedure	Mean Age years ± SD (Range)	Male sex *n* (%)	Diabetes *n* (%)	Hyper-tension, *n* (%)	Anterior Infarct, *n* (%)	Chronic renal insufficiency *n* (%)	Previous MI *n* (%)	Current smoker *n* (%)	Dyslipide-mia *n* (%)	Previous PCI *n* (%)	Previous stroke *n* (%)	Time from previous onset to index PCI *n* (%)			Killip class > 2 *n* (%)	Medications at discharge *n* (%)				
													<6 h	6-12 h	>12 h		Aspirin	P2Y12 inhibitor	Statin	Beta blockers	ACE inhibitor
Engstrom DANAMI 3 PRIMULTI	Multivessel *n* = 314	64 (37−94)	251 (80)	29 (9)	130 (41%)	105 (33)	-	17 (5)	160 (51)	-	-	-	-	-	-	22 (7)	303 (96)		310 (99)	290 (92)	142 (45)
	Culprit *n* = 313	63 (34−92)	255 (81)	42 (13)	146 (47%)	112 (36)	-	27 (9)	151 (48)	-	-	-	-	-	-	20 (6)	308 (98)		308 (98)	285 (91)	139 (44)
Ghani 2012	Multivessel *n* = 79	62 ± 10	64 (80)	5 (6.3)	21 (26.3)	17 (21.3)	-	5 (6.3)	35 (44.2)	12 (15)	3 (3.8)	0	-	-	-	1 (1.3)	-	-	-	-	-
	Culprit *n* = 41	61 ± 11	33 (80.5)	2 (5.0)	17 (42.5)	12 (29.3)	-	2 (4.9)	19 (47.5)	12 (30)	1 (2.4)	1 (2.4)	-	-	-	1 (2.4)	-	-	-	-	-
Hlinomaz PRAGUE 13 2015	Staged MV PCI *n* = 106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Culprit *n*= 108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

MV, multi vessel.

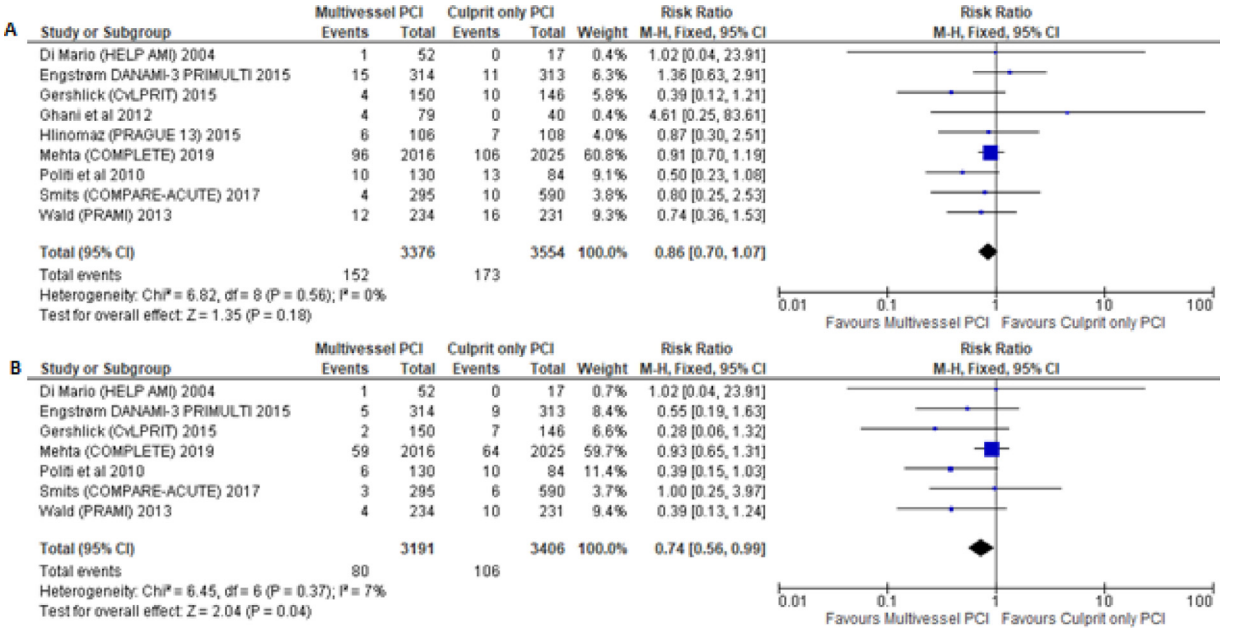

FIG 2. Forest plot for (A) all-cause mortality and (B) cardiac mortality. Summary risk ratios and 95% CIs showing no benefit of Multivessel PCI on all-cause mortality but significant benefit on cardiac mortality. CI, confidence interval; PCI, percutaneous coronary intervention.

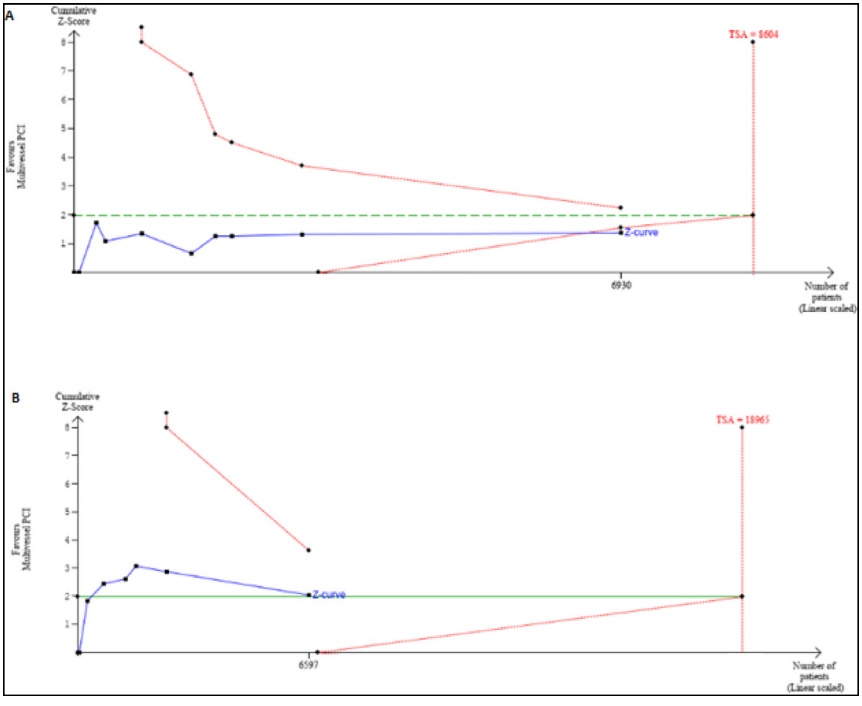

FIG 3. TSA charts for all-cause mortality (A) and cardiac mortality (B). (A) shows cumulative z line (blue) never intersecting with conventional boundary (green line) or trial sequential monitoring boundary (upper red line); but it intersects with futility boundary (red lower solid line) indicating possibly no benefit of additional studies to look for significance for this outcome. (B) shows cumulative z line marginally crossing traditional boundary of significance (green line) but not reaching trial sequential monitoring boundary (upper red line) indicating lack of robust clinical evidence of benefit. All charts are 2-sided, lower half not shown. (Color version of figure is available online.)

in the culprit only PCI group (RR 0.74, 95% CI 0.56-0.99, P= 0.04). Heterogeneity determined by I^2 and was low, hence a fixed-effects model was applied.

Figure 3 show the TSA charts for all-cause mortality and cardiac mortality. For all-cause mortality, the cumulative z-curve did not cross the conventional boundary. However, it crossed the futility boundary, indicating futility in continuing further trials to detect a 25% relative risk reduction with multivessel PCI compared to culprit only PCI. For cardiac mortality, the cumulative z-curve crossed the conventional boundary ($P = 0.05$); however, it did not cross the trial sequential monitoring boundary, indicating a lack of firm evidence for a 25% reduction in cardiac mortality with multivessel PCI when compared to culprit only PCI.

Secondary Outcomes

Secondary outcomes included reinfarction, revascularization, and MACE. The definition of MACE was not uniform across studies; some had explicitly defined it; others did not. Figure 4 shows forest plots for all components of secondary outcomes. There was a significant reduction seen in risk of reinfarction (RR 0.69, 95% CI 0.49-0.98, $P = 0.04$), the need for repeat revascularization (RR 0.36, 95% CI 0.25-0.53, $P < 0.0001$), and MACE (RR 0.58, 95% CI 0.46-0.72, $P < 0.0001$) in the patients who underwent multivessel PCI when compared to culprit only PCI.

Heterogeneity of mild to substantial level was noted in reinfarction, repeat revascularization, and MACE. For reinfarction, leave-one-out sensitivity analysis identified Ghani et al trial playing a major role in the heterogeneity, after removal of which the I^2 went down from 33% to 1%. [26] Re-analyzing the data with this trial excluded did not have a significant effect on the pooled risk ratio or significance. A random-effects model

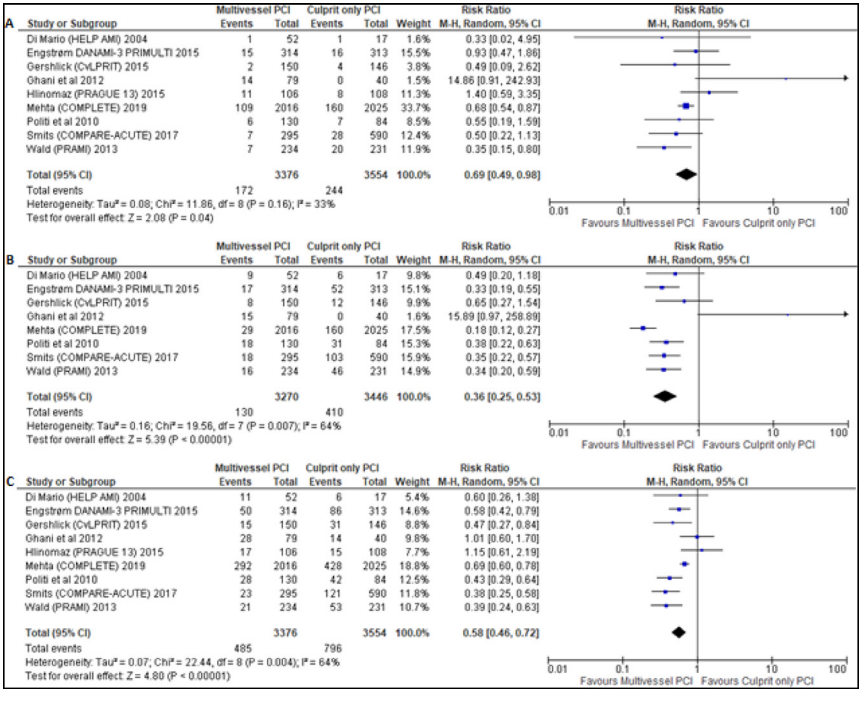

FIG 4. Forest plot for (A) reinfarction, (B) re-vascularization and (C) major adverse cardiac events (MACE). Summary risk ratios and 95% CIs showing significantly lower reinfarction, revascularization and MACE rates with Multivessel PCI. CI, confidence interval.

was applied. For the other 2 outcomes, there was no one particular study that could explain the heterogeneity by this method. However, despite several iterations of exclusions for sensitivity testing, there was no effect seen on overall effect or significance since as majority of the studies had a significant reduction in these outcome variables.

Figure 5 shows the TSA figures for reinfarction, revascularization, and MACE. The cumulative z-curve crossed the conventional boundary

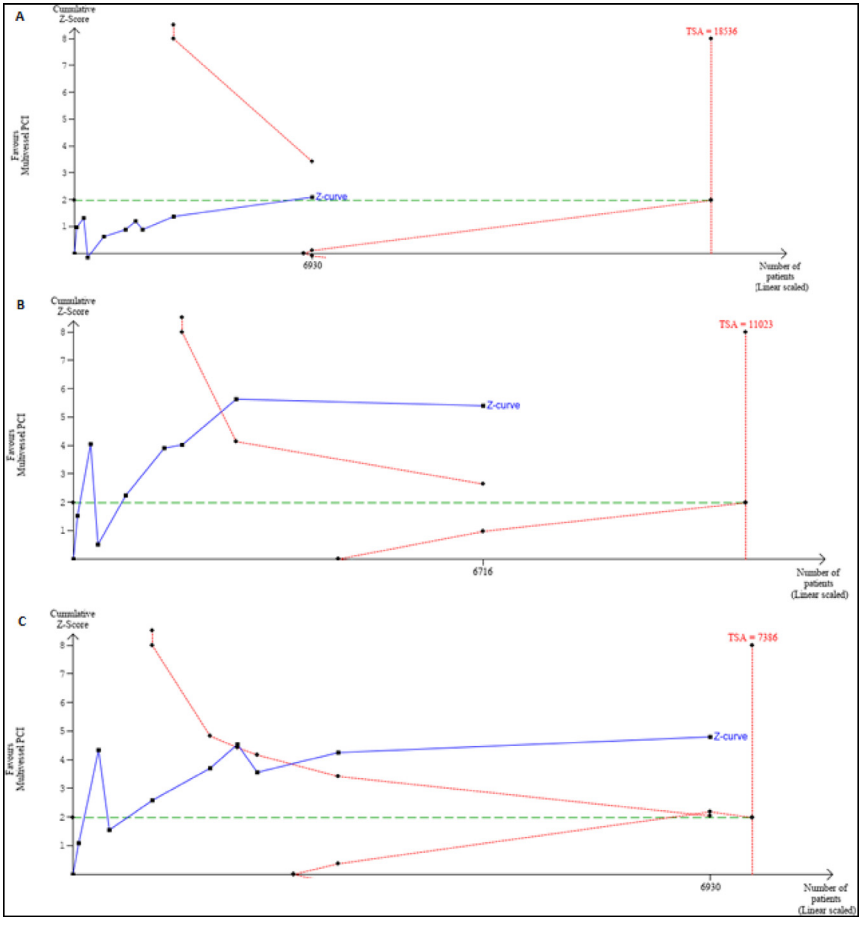

FIG 5. TSA charts for reinfarction (A), repeat revascularization (B) and MACE (C). (A) shows cumulative z line (blue) intersecting with conventional boundary (green line) but not crossing trial sequential monitoring boundary (upper red line) showing lack of robust evidence of benefit in reducing reinfarction with multivessel PCI. (B) and (C) shows cumulative z line (blue) intersecting with conventional boundary (green line) and trial sequential monitoring boundary (upper red line) showing robust evidence of benefit in reducing repeat revascularization and MACE respectively with multivessel PCI. All charts are 2-sided, lower half not shown. (Color version of figure is available online.)

($P = 0.05$) for all of these outcomes, but it crossed trial sequential monitoring boundaries only for revascularization and MACE. This shows that there is firm evidence of a 25% reduction in revascularization and MACE with multivessel PCI when compared to CO-PCI, but there is a lack of firm evidence for a 25% reduction in reinfarction per TSA.

Risk of Bias Analysis

The risk of bias for each study was performed with Cochrane Collaboration's tool, as shown in Figures 6 and 7 (Appendix1).[31] Two studies did not use satisfactory random sequence generation.[28,29] All but 2 studies were unclear about random allocation concealment.[15,24] Two studies were open-label.[27,29] As multivessel PCI and culprit only PCI are involved fundamentally different interventions apparent to the performer, none of them could have blinding of performers. Blinding of participants was also unclear for most of the studies. There was a potential attrition bias in the study by one study due to a lack of complete follow-up.[13] There was a low risk of selective reporting or other biases in all trials except one which was unclear about it.[28] One trial did not provide sufficient details to evaluate for any biases satisfactorily.[29]

Publication Bias Analysis

The publication bias in this meta-analysis was assessed by funnel plots to evaluate the reliability. However, the results of these tests are not reported, because this method is known to be unreliable when there are fewer than 10 studies in the meta-analysis.[16]

Discussion

To our knowledge, this meta-analysis and TSA contains the largest pool of data from RCTs comparing multivessel PCI vs culprit only PCI revascularization in STEMI patients without cardiogenic shock. The question of whether to perform multivessel PCI or culprit only PCI in a clinically stable patient presenting with STEMI has been a conundrum for years. Earlier observational studies suggested a trend towards harm in patients undergoing more complete revascularization.[12] Thus, ACC/AHA 2013 guidelines recommended against attempting complete revascularization in STEMI patients.[8]

The earliest RCT done by Di Mario et al included 69 patients and revealed a trend towards less need of secondary PCI after the index event in the multivessel PCI group; however, this was not statistically

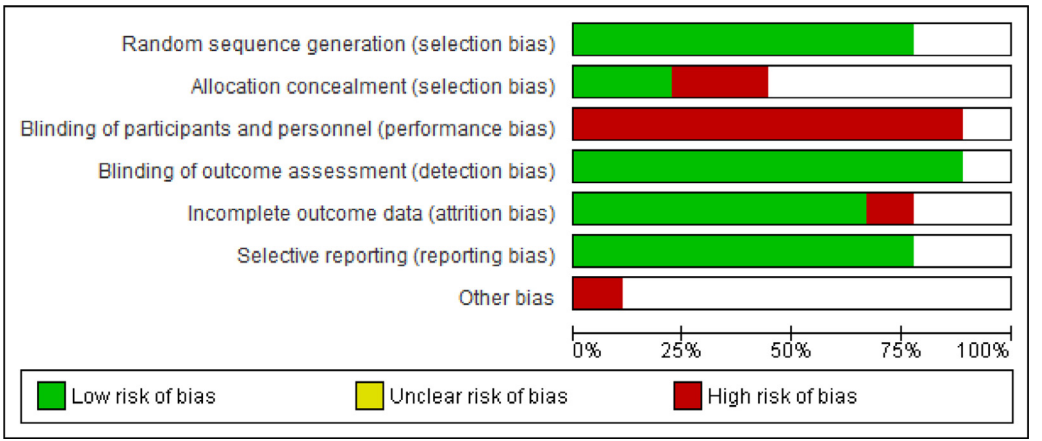

FIG 6. Risk of bias graph. Review authors' judgments about each risk of bias item presented as percentages across all included studies.

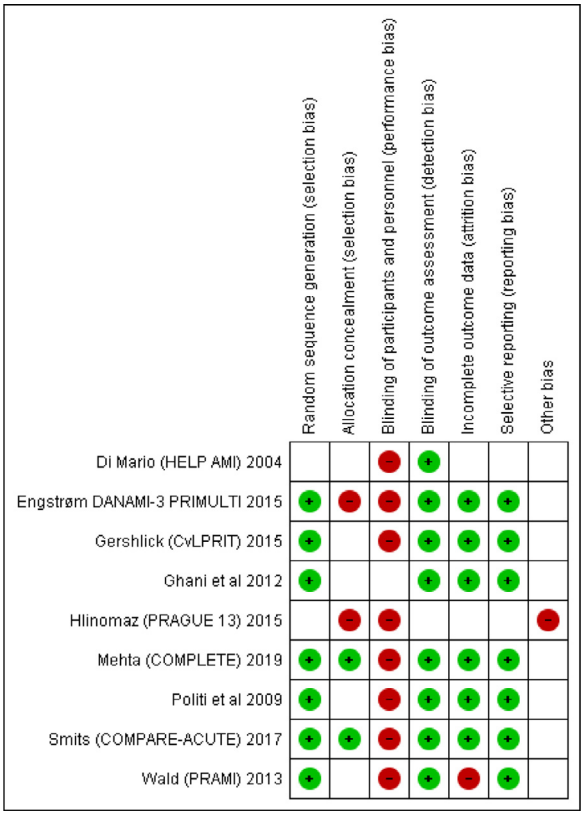

FIG 7. Risk of bias summary: Review authors' judgments about each risk of bias item for each included study.

significant.[28] Complete vs Lesion-only Primary PCI trial (CvLPRIT) enrolled 296 patients with almost equal distribution in both arms and showed all-cause mortality benefits at 12 months.[30] Similar results were seen in a RCT by Hlinomaz et al.[29] COMPLETE trial enrolled 4041 patients, of which 2016 were assigned to the complete revascularization group and 2025 to the culprit-lesion-only group over 4 years.[15] This study did not show a significant reduction in all-cause mortality with multivessel PCI approach. However, it showed a reduction in cardiovascular death and myocardial infarction. The existing data is therefore ambiguous; hence, we conducted a meta-analysis, including all the existing quality RCTs.

This meta-analysis of 9 RCTs, including 6930 patients with STEMI and multivessel disease without cardiogenic shock, demonstrates that the

risk of all-cause mortality was not significantly different between complete revascularization and culprit artery only revascularization during follow up of 12-48 months. Multivessel PCI was associated with a significant reduction in cardiac mortality as compared to the culprit artery only PCI (2.5% vs 3.1 %, $P = 0.04$). Moreover, the secondary outcomes, including the risk of reinfarction, repeat revascularization, and MACE, were all significantly lower with multivessel PCI.

The TSA provides insights into the RCT data accumulated over time. Among the 5 outcomes studied, the strongest evidence exists for all-cause mortality, revascularization, and MACE. For all-cause mortality, the curve crosses the futility threshold, indicating a low likelihood of finding evidence in favor of multivessel PCI even if more trials are conducted to increase power. For revascularization and MACE, there is convincing evidence in favor of multivessel PCI as the curves for both cross not only the conventional threshold but also the TSA thresholds. For cardiac mortality and reinfarction, the curve only crosses conventional boundaries in favor of multivessel PCI but is far from the TSA bounds. The calculated information size to be more certain for both these outcomes is almost 18,000 patients in pooled RCT; current data is limited to about 7000 patients.

Although 4 of the RCTs included in our meta-analysis have not reported a significant improvement in cardiovascular mortality, the COMPLETE trial was the biggest trial showing cardiovascular mortality benefit, which might have influenced the overall significance. Immediate complete revascularization significantly reduced the risk of reinfarction, the need for repeat revascularization, and MACE in most of the studies in this meta-analysis, which signifies the potential to significantly curb subsequent healthcare costs from recurrent hospitalizations in these patients.

The present meta-analysis includes patients who underwent single procedure multivessel PCI as well as staged multivessel PCI during the index hospitalization or just after discharge. Both these approaches appear to reduce the need for subsequent unplanned revascularization when compared to culprit only PCI ($P < 0.0001$). The only RCT, which showed an increase in repeat revascularizations, was done by Ghani et al.[26] Seven out of the 9 studies included in this analysis showed a significant improvement in the major adverse cardiac event (MACE) rates ($P < 0.0001$).

Our results are concordant to recent meta-analyses in respect to all outcomes except all-cause mortality.[32,33] The addition of the COMPLETE trial, which comprises 58% of all patients in this meta-analysis, did not

have a significant reduction in all-cause mortality, which skewed the results.

The current ACC/AHA 2015 guidelines recommend considering complete revascularization in STEMI patients without cardiogenic shock (Class IIB).[9] Similarly, the ESC 2018 guidelines recommend fractional flow reserve guided complete revascularization as well in STEMI patients without cardiogenic shock (Class IIA).[11] The results of our analysis can be helpful in analyzing the outcome of multivessel PCI vs culprit vessel only PCI and support these guidelines.

Limitations

The studies included in the meta-analysis have minor variability in their inclusion and exclusion criteria, which can lead to inherent biases of the original studies to the meta-analysis. However, the outcome data were reported homogenously; thus, results were consistent amongst all the included RCTs, as suggested by overall low heterogeneity in primary outcomes and robustness of results among secondary outcomes with moderate to high heterogeneity. The studies included were spread over 15 years, during which PCI techniques have become more advanced, and this could be a potential confounder. Admission and follow up medication data were not captured, which is also a potential confounder.

Conclusion

This is the largest meta-analysis of randomized controlled trials for multivessel PCI vs culprit only PCI in patients presenting with myocardial infarction without cardiogenic shock, revealing significantly lower cardiac mortality, reinfarction, repeat revascularization, and MACE in the multivessel PCI group. However, there was no significant difference in all-cause mortality. The results of Ffr-gUidance for compLete NoncuLprit REVASCularization (FULL REVASC -NCT02862119) will provide further insights into this conundrum regarding mortality endpoints, and may further inform guidelines and clinical practice.[34]

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Authors' contribution

Devesh Rai: Conceptualization, Methodology. ***Devesh Rai***, ***Muhammad Waqas Tahir:*** Data curation, Writing - Original draft preparation.

Dhrubajyoti Bandyopadhyay, ***Medhat Chowdhury***, ***Adnan Kharsa:*** Visualization, Investigation. ***Muhammad Waqas Tahir:*** Software, Validation. ***Srihari Naidu, Bipul Baibhav:*** Supervision, Writing - Reviewing and Editing.

Conflict of Interest

None of the authors have any conflict of interest to disclose.

REFERENCES

1. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000;343(13):915–22. https://doi.org/10.1056/NEJM200009283431303.
2. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for ac... - PubMed - NCBI. Available at: https://www-ncbi-nlm-nih-gov.ezproxy.rochesterregional.org:2443/pubmed/?term=Impact+of+multivessel+disease+on+reperfusion+success+and+clinical+outcomes+in+patients+undergoing+primary+percutaneous+coronary+intervention+for+acute+myocardial+infarction. Accessed November 21, 2019.
3. Rigattieri S, Biondi-Zoccai G, Silvestri P, et al. Management of multivessel coronary disease after ST elevation myocardial infarction treated by primary angioplasty. *J Interv Cardiol* 2008;21:1–7. https://doi.org/10.1111/j.1540-8183.2007.00317.x.
4. Hannan EL, Samadashvili Z, Walford G, et al. Culprit vessel percutaneous coronary intervention versus multivessel and staged percutaneous coronary intervention for ST-segment elevation myocardial infarction patients with multivessel disease. *JACC Cardiovasc Interv* 2010;3:22–31. https://doi.org/10.1016/j.jcin.2009.10.017.
5. Toma M, Buller CE, Westerhout CM, et al. Non-culprit coronary artery percutaneous coronary intervention during acute ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. *Eur Heart J* 2010;31:1701–7. https://doi.org/10.1093/eurheartj/ehq129.
6. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med* 1999;341:625–34. https://doi.org/10.1056/NEJM199908263410901.
7. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *J Am Med Assoc* 2006;295:2511–5. https://doi.org/10.1001/jama.295.21.2511.
8. O'Gara PTT, Kushner FGG, Ascheim DDD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:e362–425. https://doi.org/10.1161/CIR.0b013e3182742cf6.
9. Levine GNN, Bates ERR, Blankenship JCC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation

myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for t. *J Am Coll Cardiol* 2016;67:1235–50. https://doi.org/10.1016/j.jacc.2015.10.005.
10. StephanWindecker Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *Rev Esp Cardiol (Engl Ed)* 2015;68:144. https://doi.org/10.1016/j.rec.2014.12.006.
11. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)]. *G Ital Cardiol (Rome)* 2019;20:1–61. https://doi.org/10.1714/3203.31801.
12. Vlaar PJ, Mahmoud KD, Holmes DRJ, et al. Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. *J Am Coll Cardiol* 2011;58:692–703. https://doi.org/10.1016/j.jacc.2011.03.046.
13. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115–23. https://doi.org/10.1056/NEJMoa1305520.
14. Anantha Narayanan M, Reddy YN V, Sundaram V, et al. What is the optimal approach to a non- culprit stenosis after ST-elevation myocardial infarction - conservative therapy or upfront revascularization? An updated meta-analysis of randomized trials. *Int J Cardiol* 2016;216:18–24. https://doi.org/10.1016/j.ijcard.2016.04.054.
15. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2019:1411–21. https://doi.org/10.1056/nejmoa1907775.
16. Higgins JP, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (Updated July 2019)*; 2019. Cochrane www.training.cochrane.org/handbook.
17. Welch V, Petticrew M, Petkovic J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *J Clin Epidemiol* 2016;26:b2700. https://doi.org/10.1016/j.jclinepi.2015.09.001.
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100. https://doi.org/10.1371/journal.pmed.1000100.
19. Collaboration C. Review manager v5.3. *Cochrane Collab* 2014.
20. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003;327:557–60. https://doi.org/10.1136/bmj.327.7414.557.
21. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA). Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark. 2011. p. 1−115. Available from www.ctu.dk/tsa.

22. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64–75. https://doi.org/10.1016/j.jclinepi.2007.03.013.
23. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol* 2009;9:86. https://doi.org/10.1186/1471-2288-9-86.
24. Smits PC, Abdel-Wahab M, Neumann F-JJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;376:1234–44. https://doi.org/10.1056/NEJMoa1701067.
25. Politi L, Sgura F, Rossi R, et al. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. *Heart* 2010;96:662–7. https://doi.org/10.1136/hrt.2009.177162.
26. Ghani A, Dambrink JHE, van't Hof AWJ, Ottervanger JP, Gosselink ATM, Hoorntje JCA. Treatment of non-culprit lesions detected during primary PCI: long-term follow-up of a randomised clinical trial. *Netherlands Hear J* 2012;20:347–53. https://doi.org/10.1007/s12471-012-0281-y.
27. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3 - PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;386:665–71. https://doi.org/10.1016/S0140-6736(15)60648-1.
28. Di Mario C, Sansa M, Airoldi F, et al. Single vs multivessel treatment during primary angioplasty: results of the multicentre randomised HEpacoat™ for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) Study. *Int J Cardiovasc Intervent* 2004;6:128–33. https://doi.org/10.1080/14628840310030441.
29. Hlinomaz O, Groch L, Poloková K, et al. Multivessel coronary disease diagnosed at the time of primary PCI for STEMI: complete revascularisation versus conservative strategy. Prague-13 trial. *Present Eur May* 2015;17:214–20.
30. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for stemi and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015;65:963–72. https://doi.org/10.1016/j.jacc.2014.12.038.
31. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343. https://doi.org/10.1136/bmj.d5928.
32. Garcia DC, Benjo AM, White CJ, et al. Metaanalysis of multivessel vs culprit artery only percutaneous coronary intervention in ST elevation myocardial infarction. *Ochsner J* 2019;19:107–15. https://doi.org/10.31486/toj.18.0033.
33. Bangalore S, Toklu B, Stone GW. Meta-analysis of culprit-only versus multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction and multivessel coronary disease. *Am J Cardiol* 2018;121:529–36. https://doi.org/10.1016/j.amjcard.2017.11.022.
34. Ffr-gUidance for compLete Non-cuLprit REVASCularization (FULL REVASC). https://clinicaltrials.gov/ct2/show/NCT02862119.