ORIGINAL RESEARCH

Comparison of Approaches to Revascularization in Patients With Multivessel Coronary Artery Disease Presenting With ST-Segment Elevation Myocardial Infarction: Meta-analyses of Randomized Control Trials

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***Background*—**Significant controversy exists regarding the best approach for nonculprit vessel revascularization in patients with multivessel coronary artery disease presenting with ST-segment elevation myocardial infarction. We conducted a systematic investigation to pool data from current randomized controlled trials (RCTs) to assess optimal treatment strategies in this patient population.

***Methods and Results*—**A comprehensive search of SCOPUS from inception through May 2015 was performed using predefined criteria. We compared efficacy and safety outcomes of different approaches by categorizing the studies into 3 groups: (1) complete revascularization (CR) versus culprit lesion revascularization (CL) at index hospitalization, (2) CR at index hospitalization versus staged revascularization (SR) of nonculprit vessels at a separate hospitalization, and (3) comparison of SR versus CL. Eight eligible RCTs met the inclusion criteria: (1) CR versus CL (6 RCTs, n=1727) (2) CR versus SR (3 RCTs, n=311), and (3) SR versus CL (1 RCT, n=149). We observed significantly lower rates of major adverse cardiovascular events, revascularization, and repeat percutaneous coronary interventions among patients treated with CR and SR compared with a CL approach ($P<0.05$). The rates of all-cause mortality, cause-specific mortality, major bleeding, reinfarction, stroke, and contrast-induced nephropathy did not differ in the CR arm compared with the CL arm. The rates of these outcomes were similar in the CR and SR arms.

***Conclusion*—**Results suggest that CR and SR compared with CL reduce major adverse cardiovascular event and revascularization rates primarily by lowering repeated percutaneous coronary intervention rates. We did not observe any increase in the rate of adverse events while using a CR or SR strategy compared with a CL approach. Current guidelines discouraging CR need to be reevaluated, and clinical judgment should prevail in treating multivessel coronary artery disease patients with ST-segment elevation myocardial infarction as data from larger RCTs accumulate. **(*J Am Heart Assoc*. 2015;4:e002540 doi: 10.1161/JAHA.115.002540)**

Key Words: complete revascularization • culprit lesion • percutaneous coronary intervention • ST-segment elevation myocardial infarction

ST-segment elevation myocardial infarction (STEMI) is the one of the most dreadful consequence of advanced atherosclerosis and remains a challenge despite major advances in the field. Data from large-scale observational studies and multiple acute coronary syndrome registries suggest that disease in the "noninfarct" artery is very

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Accompanying Tables S1 through S3 and Figures S1 through S5 are available at http://jaha.ahajournals.org/content/4/12/e002540/suppl/DC1

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common in patients presenting with STEMI and is associated with worse outcomes.[1–4] Multiple treatment strategies have been described, including multivessel percutaneous coronary intervention (PCI) at the time of the index procedure, staged PCI of nonculprit vessels guided by hemodynamic assessment, and a conservative approach with primary PCI of only the culprit lesion and subsequent medical therapy unless recurrent ischemia occurs.[5]

The current American College of Cardiology and American Heart Association guidelines favor the conservative approach and discourage complete revascularization (CR) at the time of index left-heart catheterization.[6] The European Society of Cardiology and the European Association for Cardio-Thoracic Surgery also discourage CR at the time of index catheterization but recommend staged PCI in patients with evidence of recurrent ischemia.[5,7] These recommendations were primarily based on observational studies and inadequately powered small randomized controlled trials (RCTs) that demonstrated lack of safety and benefit of CR in patients with multivessel coronary artery disease presenting with STEMI.[8–12]

Three large-scale RCTs[13–15] comparing CR at index hospitalization versus culprit lesion revascularization (CL) were published recently. All reported varying degrees of benefit for multiple cardiovascular end points favoring CR as a strategy. RCTs have compared staged revascularization (SR) at a time after the index hospitalization with CR[16–18] and with CL,[17] with conflicting data regarding efficacy and safety outcomes when using these strategies in STEMI patients. Given the absence of definitive clinical trial data regarding the best approach for nonculprit revascularization in these patients, we conducted the current investigation of systematically pooling data from all available RCTs (1) to check for concordance with the current guidelines and (2) to evaluate an optimal treatment strategy with respect to both efficacy and safety in such clinical scenarios.

Methods

Study Inclusion and Exclusion Criteria

This systematic review was performed according to the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19] RCTs published between 1966 and May 2015 that reported the effects of various revascularization strategies in adult patients presenting with STEMI were identified and analyzed using the following a priori defined inclusion criteria: (1) The study included randomized controlled experiments that compared clinical outcomes of different approaches for nonculprit vessel PCI in patients with STEMI, and (2) the study reported data on the incidence of desired postprocedural clinical end points including all-cause mortality, reinfarction, revascularization, cardiovascular mortality, need for repeat PCI, need for repeat coronary artery bypass grafting (CABG), stroke, contrast-induced nephropathy (CIN),[20] and major bleeding. The primary outcome of interest was a composite of all-cause mortality during follow-up, reinfarction, and revascularization, defined as major adverse cardiovascular events (MACE). The definitions of these end points are presented in Table S1. Studies not including a control group, animal studies, imaging studies, or trials that solely reported nonclinical outcomes were excluded. Case reports, editorials, comments, letters, review articles, guidelines, and non-STEMI trials were also excluded from the analysis.

Search Strategy and Quality Assessment

Two authors (N.S.B. and P.A.) independently performed an electronic literature search in SCOPUS[21] (which includes Medline, Embase, Compendex, World Textile Index, Fluidex, Geobase, and Biobase) using a predefined list of keywords, which were verified by a third investigator (R.K.) (Supplement Section 1). All English-language human studies published in full-text or abstract form were eligible for inclusion. In addition, abstracts and oral presentations from the European Association of Cardiothoracic Surgery, the Society of Thoracic Surgeons, the European Society of Cardiology, the American Association of Thoracic Surgery, the American Heart Association, the American College of Cardiology, the American Society of Anesthesiologists, and the Society of Cardiovascular Anesthesiology were screened by searching the individual websites and corroborated by our SCOPUS search. All titles and abstracts from the electronic search were uploaded into a reference management software database. After initial abstract review, all potentially relevant studies were identified, and the full-text publications were retrieved for detailed evaluation. When >1 publication from the same patient population existed, then the study with the most complete data set was included for meta-analysis. Furthermore, reference lists of potentially relevant reports and reviews were screened to identify other eligible studies. Data were extracted and quality was assessed for all information regarding authorship, year of publication, type of publication (abstract, full-text manuscript), study design (RCT, observational study), study population (clinical and procedural characteristics), length of follow-up, and clinical end points. Methodological quality of the included studies was assessed by 2 independent investigators (N.S.B, R.K) using the Jadad score[22] for RCTs. The Jadad score is a validated 5-point scale (0–2: poor quality; 3–4: good quality; 5: excellent quality) that examines the methods of randomization, double blinding, and reporting of dropouts. All discrepancies in data extraction were resolved by consensus. The consensus process to resolve disagreements required investigators to discuss the

decisions at weekly meetings, with mandatory recognition of errors by 1 of the reviewers.

Statistical Analysis

Statistical analyses were performed using Comprehensive Meta-Analysis version 2.2.046 (Biostat) and Stata 14.0 (StataCorp). Comprehensive statistical analyses were done in accordance with the PRISMA statement.[23] The studies were categorized into 3 groups. The first group compared CR versus CL at index left-heart catheterization or at repeat left-heart catheterization a few days later during same hospitalization, with hemodynamic assessment via fractional flow reserve (FFR). The second group compared CR at index hospitalization versus SR of nonculprit vessels at a separate hospitalization. The third group compared SR and CL. The relative risk (RR) ratio was chosen as the principal measure of effect because the unit of measurement was similar across all studies. A random-effects model was used to estimate summary measures of association. Data were analyzed for heterogeneity using the I^2 statistic proposed by Higgins and Thompson.[24] We conducted a prespecified subgroup analysis for MACE in the CR versus CL group, stratifying the group by FFR utilization to assess hemodynamic significance of the nonculprit lesions versus nonutilization. Publication bias for the CR versus CL group was assessed and quantified using Egger's regression intercept.[25] A 2-sided $P<0.05$ was considered statistically significant except in Egger's test (in which a 1-sided $P<0.05$ was defined as significant). Correction for publication bias was performed using the trim-and-fill method, described by Duval and Tweedie,[26] that approximates the number of unpublished studies needed to achieve symmetry of the funnel plot, thereby recalculating an adjusted RR. We also conducted a network meta-analysis using a multivariate random-effects model described by White et al and Chaimani et al,[27,28] using the *mvmeta* command in Stata 14.0 running both consistency and inconsistency models.

Results

Our initial search identified 739 studies, of which 8[13–18,29,30] were included in the final analysis (Figure 1). The meta-analysis has been reported in accordance with PRISMA guidelines (Table S2). These studies were divided into 3 categories: (1) CR versus CL (6 RCTs, n=1727), (2) CR versus SR (3 RCTs, n=311), and (3) SR versus CL (1 RCT, n=149). All studies had at least 6 months of follow-up, with a range of 6 to 36 months. The main demographic and procedural characteristics of the studies are shown in Tables 1 and 2. None of the studies were blinded. In the CR versus CL group, 2 of 6 studies[15,30] used FFR assessment prior to PCI. The use of drug-eluting stents was variable among the studies (Table 2). The incidence of 2- versus 3-vessel disease was reported in 4 of 8 studies, and more patients were likely to have 2-vessel disease (Table 2). The use of different periprocedural pharmacotherapies was variable among studies and is outlined in Table 2. The mean contrast volume in the CR and SR arms was higher than in CL arms in corresponding RCTs (Table 2). The Jadad quality score was good for 4 trials[13,15,17,30] and poor for 4 RCTs[15,16,18,29] (Table 3). All studies reported MACE, all-cause mortality, reinfarction, and revascularization. Other outcomes were reported variably by studies and are outlined in Table S3.

Outcomes for CR Versus CL

Efficacy outcomes

Six studies reported MACE (Table S3) in patients undergoing CR (n=895) compared with CL (n=832). The pooled results showed that MACE was lower in patients who underwent CR compared with CL (RR 0.54, 95% CI 0.54 to 0.93, $P<0.001$) (Figure 2 and Table 4). The incidence rate of MACE remained low in the CR arm (n=501) compared with the CL arm (n=478) for 4 studies that did not have FFR assessment prior to CR (RR 0.43, 95% CI 0.34 to 0.55, $P<0.001$). In the 2 studies using FFR assessment[15,28] prior to CR (n=394), the MACE rates were similar to those of the CL arm (n=354) (RR 0.75, 95% CI 0.44 to 1.29, $P=0.30$).

Six studies (Table S3) reported all-cause mortality in patients undergoing CR (n=895) and CL (n=832). The pooled results showed no difference in all-cause mortality for patients who underwent CR or CL (RR 0.81, 95% CI 0.53 to 1.25, $P=0.34$) (Table 4). Four of these 6 studies (Table S3) reported cardiovascular mortality. We observed no difference in cardiovascular mortality in patients undergoing CR (n=763) compared with CL (n=774) (RR 1.07, 95% CI 0.69 to 1.67, $P=0.30$) (Table 4).

Six studies reported revascularization (Table S3) in patients undergoing CR (n=895) and CL (n=832). The rates of revascularization were significantly lower in patients undergoing CR versus CL (RR 0.45, 95% CI 0.29 to 0.68, $P<0.001$) (Table 4). The lower rate of revascularization in the CR arm was driven by lower rates of repeat PCI in the CR arm compared with the CL arm (RR 0.39, 95% CI 0.25 to 0.61, $P<0.001$). The rates of repeat CABG were similar across arms (RR 1.05, 95% CI 0.19 to 5.80, $P=0.96$) (Table 4).

Six studies reported reinfarction in patients undergoing CR (n=895) and CL (n=832). The pooled results showed that reinfarction rates were similar in patients undergoing CR and CL (RR 0.63, 95% CI 0.30 to 1.31, $P=0.22$) (Table 4).

Safety outcomes

Safety outcomes were reported variably among studies (Table S3). We observed no difference in stroke rate, CIN, and major bleeding in patients undergoing CR compared with

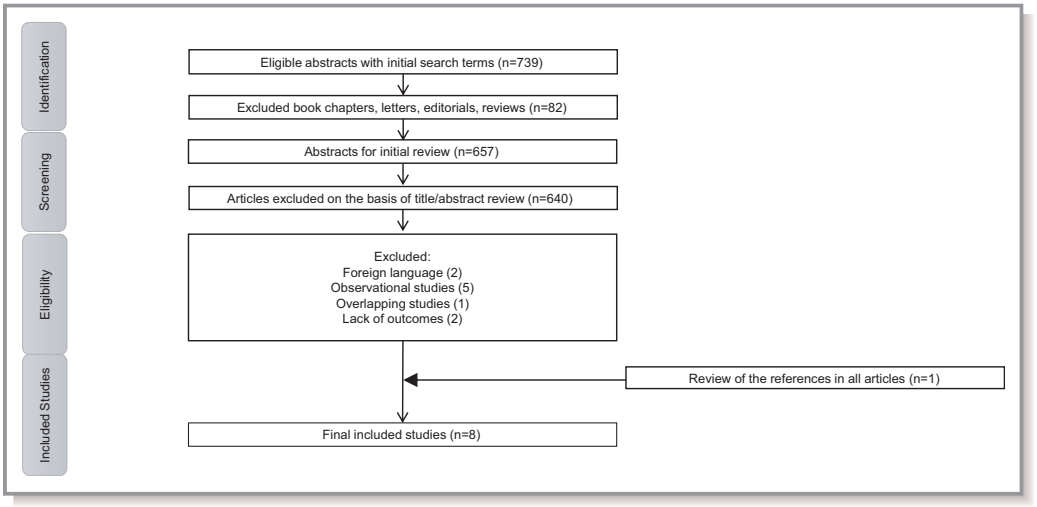

Figure 1. Flow diagram for study selection.

CL. Risk ratios for stroke, CIN, and major bleed for CR compared with CL were 2.19 (95% CI 0.59 to 8.12), 0.71 (95% CI 0.31 to 1.59), and 0.72 (95% CI 0.34 to 1.54), respectively.

Outcomes for CR Versus SR

Efficacy outcomes

Three studies reported rates of MACE, revascularization, reinfarction, all-cause and cardiovascular mortality, and the need for repeat PCI. Two of 3 studies reported the need for repeat CABG (Table S3) in patients undergoing CR (n=159) compared with SR (n=152). The pooled results showed that all efficacy outcomes were similar in patients undergoing CR compared with SR. The risk ratios for these outcomes are reported in Table 4.

Safety outcomes

Safety outcomes were reported variably among studies (Table S3). We observed no difference in CIN and major bleed in patients undergoing CR compared with SR (Table 5).

Outcomes for SR Versus CL

Efficacy outcomes

Only 1 study[17] compared efficacy outcomes and reported MACE, revascularization, reinfarction, all-cause and cardiovascular mortality, need for repeat PCI, and need for repeat CABG (Table S3) in patients undergoing SR (n=65) compared with CL (n=84). The pooled results showed that MACE, revascularization, and repeat PCI were lower in the SR arm than the CL arm (Table 4). The rates of all-cause and cardiovascular mortality, reinfarction, and repeat CABG were similar in patients undergoing SR compared with CL.

Safety outcomes

Safety outcomes were reported variably among studies (Table S3). We observed no difference in CIN in patients undergoing SR compared with CL (Table 5).

Publication Bias Assessment

The studies reporting the primary outcome (MACE) in the CR and CL groups were distributed symmetrically on visual examination of the funnel plot (Figure 3), and Egger's weighted regression statistic (P=0.35) indicated no significant publication bias. Although there was significant publication bias in the CR versus SR group (P=0.002), the adjusted RR using trim and fill was not significantly different from the unadjusted RR.

Network Meta-analysis Results

We compared the aforementioned treatment strategies using network meta-analysis. There were 8 studies with 10 direct comparisons (Figure S1). The comparison of CR versus CL contributed most to the network (Figure S2). There was no inconsistency across 3 treatment strategies as determined by the inconsistency model (Figures S3 and S4). CR and SR appeared better at reducing MACE than CL (Figure S4). Figure S5 shows the funnel plot for the treatment network. These results are consistent with the conventional meta-analyses presented.

Discussion

Our meta-analyses showed that patients with multivessel coronary artery disease presenting with STEMI treated with different strategies, as described, have different risk profiles and outcomes. Patients undergoing CR compared with CL had

Table 1. Baseline Characteristics of Included Studies

Study Name/First Author	Publication Year of Study	Number of Patients	Age Mean, Years	Sex (Male)	Hypertension	Diabetes	Dyslipidemia	Smoking	Previous MI	SBP	DBP	Infarct Location: Anterior	Two-Vessel Disease	Three-Vessel Disease	Follow-up, Months
RCTs with CR vs CL at time of index catheterization or staged at index hospitalization															
CvLPRIT/ Gershlick et al[14]	2015	150/146	65/65	128/112	54/51	19/20	41/34	50/37	7/5	NR	NR	54/52	119/110	31/36	12
DANAMI3-PRIMULTI/ Engstrøm et al[15]	2015	314/313	64/64	251/255	130/146	29/42	NR	160/151	17/27	NR	NR	105/112	NR	NR	12
PRAMI/Wald et al[13]	2013	234/231	62/62	177/186	94/93	35/48	NR	118/103	19/16	136/134	81/80	67/89	143/155	91/76	23
Dambrink et al[30]	2010	80/41	62/61	64/33	21/17	5/2	12/12	35/19	5/2	132/137	78/84	NR	60/33	20/8	6
HELP-AMI/Di Mario et al[29]	2004	52/17	64/65	46/14	19/10	6/7	22/9	35/14	NR	136/141	83/85	27/10	36/9	16/8	12
RCTs with CR vs SR after the index hospitalization															
Tarasov et al[16]	2014	46/43	59/59	32/25	44/37	12/9	NR	NR	5/2	NR	NR	NR	NR	20/20	6
PRIMA/Ochala et al[18]	2004	48/44	65/67	35/33	25/21	15/15	39/40	18/19	14/10	115/112	NR	22/20	NR	NR	6
RCT with CR vs CL vs SR after the index hospitalization															
Politi et al[17]	2010	65/84/65	65/67/64	50/64/52	32/50/42	9/20/12	NR	NR	NR	136/136/136	NR	31/35/38	NR	19/21/29	36

CL indicates culprit lesion revascularization; CR, complete revascularization; CvLPRIT, Randomized Trial of Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease; DANAMI3-PRIMULTI, The Third DANish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction PRImary PCI in MULTIvessel Disease; DBP, diastolic blood pressure; HELP-AMI, HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction; MI, myocardial infarction; NR, not reported; PRAMI, Randomized Trial of Preventive Angioplasty in Myocardial Infarction; PRIMA, PRIMAry percutaneous intervention for acute myocardial infarction; RCTs, randomized controlled trials; SBP, systolic blood pressure; SR, staged revascularization.

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Table 2. Procedural and Pharmacological Treatment Characteristics of Included Studies

Study Name/First Author	Publication Year of Study	Number of Patients	Mean Procedure Duration (Minutes)	Mean Contrast Volume (mL)	PCI With DES	GPIIb/IIIa	Aspirin	Clopidogrel, Prasugrel, or Ticagrelor	BB	Statin	ACEI or ARB
RCTs with CR vs CL at time of index catheterization or staged at index hospitalization											
CvLPRIT/Gershlick et al[14]	2015	150/146	55/41	250/190	141/127	46/44	141/131	136/136	137/126	146/133	142/129
DANAMI3-PRIMULTI/Engstrøm et al[15]	2015	314/313	76/42	280/170	298/290	64/72	303/308	310/309	290/285	310/308	142/139
PRAMI/Wald et al[13]	2013	234/231	63/45 (median)	300/200 (median)	NR	178/176	233/229	234/229*	207/210	222/223	218/209
Dambrink et al[30]	2010	80/41	NR	NR	18/7	36/19	NR	NR	NR	NR	NR
HELP-AMI/Di Mario et al[29]	2004	52/17	69/53	341/242	NR	39/14	NR	NR	NR	NR	NR
RCTs with CR vs SR after the index hospitalization											
Tarasov et al[16]	2014	46/43	NR	314/354	46/43	NR	NR	NR	NR	NR	NR
PRIMA/Ochala et al[18]	2004	48/44	66/84	316/244	NR	25/22	NR	48/44*	NR	NR	NR
RCT with CR vs CL vs SR after the index hospitalization											
Politi et al[17]	2010	65/84/65	NR	NR	5/10/6	NR	62/74/65	61/71/65*	52/62/52	57/68/60	35/48/38

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; BB, beta blocker; CL, culprit lesion revascularization; CR, complete revascularization; CvLPRIT, Randomized Trial of Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease; DANAMI3-PRIMULTI, The Third DANish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction PRImary PCI in MULTIvessel Disease; DES, drug-eluting stent; GPIIb/IIIa, glycoprotein IIb/IIIa inhibitor; HELP-AMI, HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction; NR, not reported; PCI, percutaneous coronary intervention; PRAMI, Randomized Trial of Preventive Angioplasty in Myocardial Infarction; PRIMA, PRIMAry percutaneous intervention for acute myocardial infarction; RCTs, randomized controlled trials; SR, staged revascularization.
*Only clopidogrel use was reported.

significantly lower rates of MACE, revascularization, and repeat PCI. The rates of all-cause and cardiovascular mortality, reinfarction, and repeat CABG were similar in patients undergoing CR and CL. In CR versus CL, the benefits of these efficacy outcomes were not outweighed by an increase in adverse events such as stroke, CIN, or major bleeding. Similar

Table 3. Quality Assessment of Included Randomized Control Trails by Jadad Scale (Score 1–5)

Study Name/First Author (References)	Randomization (2)	Blinding (2)	Withdrawal and Dropouts (1)	Total Score
CvLPRIT/Gershlick et al[14]	1+1	1 (Open label)	1	4
PRAMI/Wald et al[13]	1+1	1 (Open label)	1	4
HELP-AMI/Di Mario et al[29]	1	1 (Open label)	0	2
DANAMI3-PRIMULTI/Engstrøm et al[15]	1	1 (Open label)	1	2
Dambrink et al[30]	1+1	1 (Open Label)	1	4
Politi et al[17]	1+1	1 (Open label)	0	3
PRIMA/Ochala et al[18]	1	0 (Open label)	0	1
Tarasov et al[16]	1	0 (Open label)	1	2

CvLPRIT indicates Randomized Trial of Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease; DANAMI3-PRIMULTI, The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction PRImary PCI in MULTIvessel Disease; HELP-AMI, HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction; PRAMI, Randomized Trial of Preventive Angioplasty in Myocardial Infarction; PRIMA, PRIMAry percutaneous intervention for acute myocardial infarction.

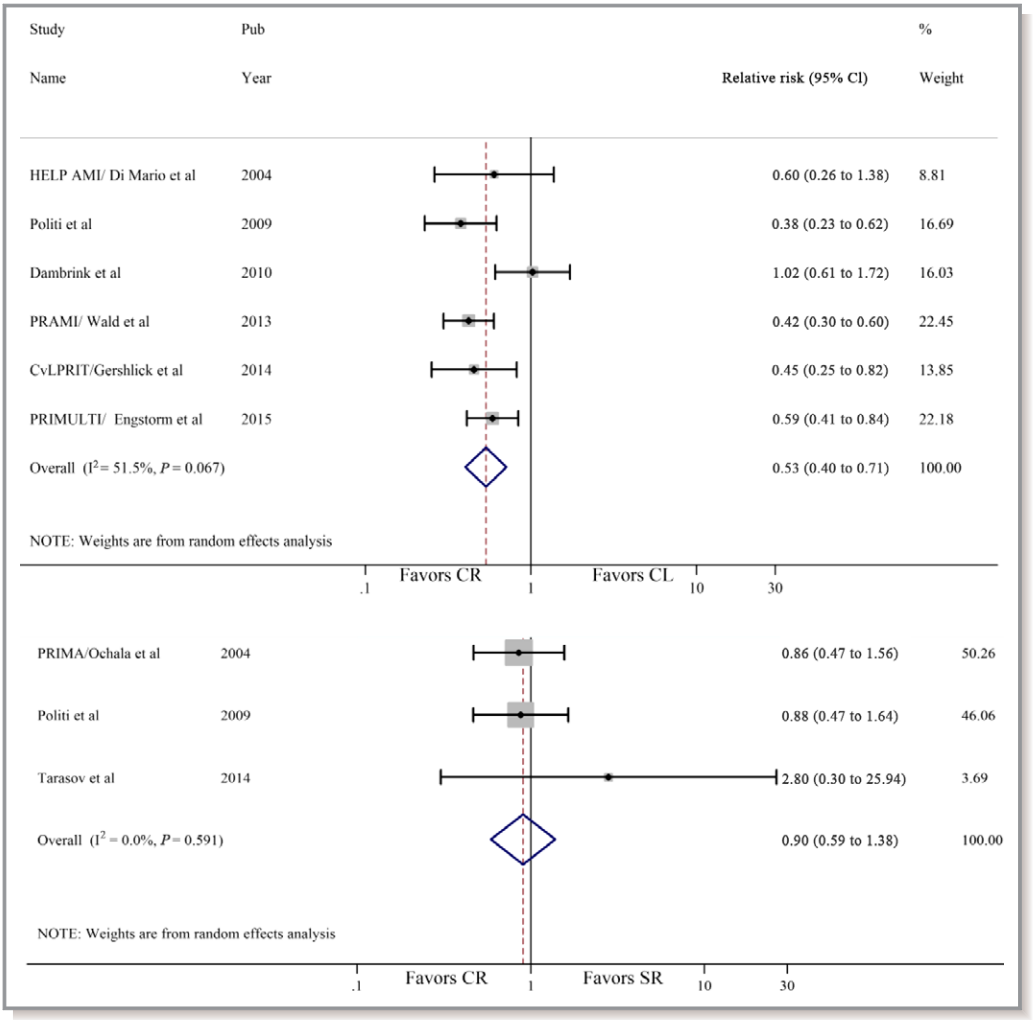

Figure 2. Forest plots depicting risk ratios for major adverse cardiovascular events for 2 strategies. The black diamond is the point estimate with the line representing the 95% CI. The size of the gray box reflects the weight of the study. The blue diamond represents the random-effects–generated overall estimate. CL indicates culprit lesion revascularization; CR, complete revascularization; CvLPRIT, Randomized Trial of Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease; HELP-AMI, HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction; PRAMI, Randomized Trial of Preventive Angioplasty in Myocardial Infarction; PRIMULTI, The Third Danish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction PRImary PCI in MULTIvessel Disease; PRIMA, PRIMAry percutaneous intervention for acute myocardial infarction; Pub, publication; RR, relative risk; SR, staged revascularization.

results in efficacy and safety outcomes were observed in patients undergoing SR compared with CL. Efficacy and safety outcomes (CIN and major bleed) did not differ between the CR and SR arms. Among patients undergoing CR and using FFR assessment prior to CR, we observed a nonsignificant trend toward lower MACE rates compared with the CL approach.

STEMI is a heightened inflammatory state with a prothrombotic component. This concept was thought to explain the higher rates of periprocedural myocardial infarction and increased rates of late revascularization secondary to restenosis in patients undergoing CR.[4,17,29,31,32] Consequently, the conventional approach for decades has been based on the principle that "less is more" when it comes to nonculprit vessel PCI. The understanding that increased circulating catecholamines in the setting of STEMI leads to vasoconstriction, thereby exaggerating the severity of nonculprit lesions, has primarily driven this "do less" approach.[33] In the meta-analyses presented, our observations contrasted with those above. The rates of MACE, revascularization, and repeat PCI were lower in patients undergoing CR and SR compared with CL. These rates seemed to be driven by increased repeat PCI in patients undergoing CL only at the time of index left-heart catheterization; rates of all-cause mortality, reinfarction, and repeat CABG were similar when

Table 4. Efficacy Outcomes of Different Treatment Strategies in Patients With Multivessel Coronary Artery Disease Presenting With ST-Segment Elevation Myocardial Infarction

Efficacy Outcomes	Number of RCTs	Number of Patients, Group 1/Group 2	Number of Events, Group 1/Group 2	Risk Ratio (95% CI) Random-Effects Modeling
CR vs CL at time of index catheterization or staged at index hospitalization				
MACE	6	895/832	142/248	0.54 (0.40–0.71)
Revascularization	6	895/832	83/162	0.45 (0.29–0.68)
All-cause mortality	6	895/832	42/50	0.81 (0.53–1.25)
Cardiovascular mortality	4	763/774	36/36	1.07 (0.69–1.67)
Reinfarction	6	895/832	41/48	0.63 (0.30–1.31)
Repeat PCI	3	459/438	35/83	0.39 (0.25–0.61)
Repeat CABG	3	459/438	16/11	1.05 (0.19–5.80)
CR vs SR after the index hospitalization				
MACE	3	159/152	31/32	0.90 (0.59–1.38)
Revascularization	3	159/152	19/19	0.91 (0.51–1.62)
All-cause mortality	3	159/152	6/5	1.23 (0.39–3.82)*
Cardiovascular mortality	3	159/152	4/2	2.0 (0.38–10.54)†
Reinfarction	3	159/152	8/8	0.83 (0.27–2.57)
Repeat PCI	2	113/109	4/17	0.22 (0.02–2.51)
Repeat CABG	2	113/109	2/2	1.0 (0.83–1.20)
SR after the index hospitalization vs CL‡				
MACE	1	65/84	16/48	0.43 (0.27–0.69)
Revascularization	1	65/84	8/28	0.37 (0.18–0.76)
All-cause mortality	1	65/84	4/13	0.40 (0.14–1.16)
Cardiovascular mortality	1	65/84	2/10	0.26 (0.06–1.14)
Reinfarction	1	65/84	4/7	0.74 (0.23–2.42)
Repeat PCI	1	65/84	7/25	0.36 (0.17–0.78)
Repeat CABG	1	65/84	2/3	0.86 (0.15–5.00)

CABG indicates coronary artery bypass grafting; CL, culprit lesion revascularization; CR, complete revascularization; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials; SR, staged revascularization.

*Only 2 studies were used to estimate the risk ratio because there were no all-cause deaths in both groups in Ochala et al.

†Only 1 study was used to estimate the risk ratio because there were no cardiovascular deaths in both groups in Ochala et al and Tarasov et al.

‡Only Politi et al compared this approach.

comparing CR and SR with CL. These findings may be explained by the fact that patients with STEMI can have several unstable plaques involving nonculprit vessels. The lack of revascularization of these unstable plaques may lead to increased adverse events. In addition, severe disease in nonculprit vessels may hamper myocardial contractility and may impair collateral development, leading to increased incidence of revascularization (repeat PCI) in patients treated with CL.[4,17,29,32]

Furthermore, we designed our systematic investigation not only to address the efficacy of an optimal revascularization approach of nonculprit vessels but also to closely examine the safety of such an approach. We hypothesized that CR and SR instead of CL may lead to prolonged interventions, multiple catheter manipulations with increased risk of stroke, increased use of contrast, heart failure, and renal impairment. We found that the procedural times and contrast load were higher in patients undergoing CR and SR compared with CL. The rates of stroke, CIN, and major bleeds, however, were not different from the CL arm, indicating that the need for repeat PCI during follow-up among patients undergoing CL may have balanced out these adverse events in the 2 groups.

Similar rates of efficacy and safety outcomes in patients undergoing CR compared with SR may suggest that timing of revascularization is not as important as the need for revascularization; however, this needs to be addressed in a larger prospective clinical trial with timing of revascularization as the primary variable.

Table 5. Safety Outcomes of Different Treatment Strategies in Patients With Multivessel Coronary Artery Disease Presenting With ST-Segment Elevation Myocardial Infarction

Safety Outcomes	Number of RCTs	No. of Patients, Group 1/Group 2	Number of Events, Group 1/Group 2	Risk Ratio (95% CI) Random-Effects Modeling
CR vs CL at time of index catheterization or staged at index hospitalization				
Stroke	3	698/690	8/3	2.19 (0.59–8.12)
CIN	4	763/774	10/15	0.71 (0.31–1.59)
Major bleed	3	698/690	12/17	0.72 (0.34–1.54)
CR vs SR after the index hospitalization				
Stroke	NR	NR	NR	NR
CIN	1	65/84	1/2	0.50 (0.05–5.38)*
Major bleed	1	48/44	0/0	N/A
SR after the index hospitalization vs CL				
Stroke	NR	NR	NR	NR
CIN	1	65/84	2/3	0.86 (0.15–5.00)
Major bleed	NR	NR	NR	NR

CIN indicates contrast-induced nephropathy; CL, culprit lesion revascularization; CR, complete revascularization; N/A, not applicable—cannot be calculated because there were no events; NR, not reported; RCTs, randomized controlled trials; SR, staged revascularization.
*Only Politi et al reported this comparison.

To our knowledge, ours is the first and largest meta-analysis of RCTs comparing various approaches to nonculprit vessel revascularization in patients with multivessel coronary artery disease presenting with STEMI, in addition to looking at the safety outcomes of such approaches. Few meta-analyses addressing the clinical question of nonculprit vessel revascularization have been published, but they are limited by noninclusion of all newer RCTs[15]; by misclassification of observational studies as RCTs; and by pooling of data with different strategies, namely, CR at time of index catheterization with or without FFR guidance and SR versus CL.[34–37] In addition, none of these meta-analyses have reported data on safety outcomes of different revascularization approaches of nonculprit vessels.

Our meta-analyses suggest that patients undergoing CR and SR may benefit in terms of lower rates of MACE, revascularization, and repeat PCI without any increase in adverse events. Such an approach to nonculprit vessel revascularization may also limit vascular access and anticoagulant-related bleeding complications arising from further procedures, thereby potentially reducing hospitalization costs. The results of our meta-analyses are in concordance with the 3 most recent and largest RCTs,[13–15] indicating the internal consistency of our data. Adding to the accumulating evidence in the literature, results from our meta-analyses strongly raise the possibility that CR compared with CL is not only efficacious but also safe as a treatment strategy in patients with multivessel coronary artery disease presenting with STEMI.

Study Limitations

Several limitations deserve comment. First, the validity of our results is dependent on the validity of the studies included. Second, the potential limitation of these meta-analyses could be the small number of included RCTs, which accurately reflect the current body of evidence. Third, due to the nature of the disease, blinding was not possible, and availability of this information to patients and providers about unrevascularized coronary lesions could have driven some of the future revascularization procedures among patients randomized to a culprit-only strategy and may have introduced a bias. Fourth, we included data that were reported only in conference presentations or in abstract form.[15] This inclusion was necessary to maximize the use of all available data on this important topic and to present an updated and comprehensive review of the literature. Fifth, treatment decisions were not based on assessing hemodynamic significance of nonculprit lesions by stress testing or FFR in all RCTs and that may have led to even higher rates of repeat PCI in patients undergoing CR or SR compared with CL. We also observed a higher RR in our stratified analysis of the subgroup of the CR arm in which FFR was used. This is a potential source of heterogeneity. Nevertheless, there is conflicting evidence in the literature regarding the use of FFR-guided revascularization[38–43] in patients with STEMI, and the validity of FFR in this setting needs to be established in future prospective studies. Sixth, the studies varied in terms of duration of follow-up (range 6 to 36 months), design, and definition of MACE and

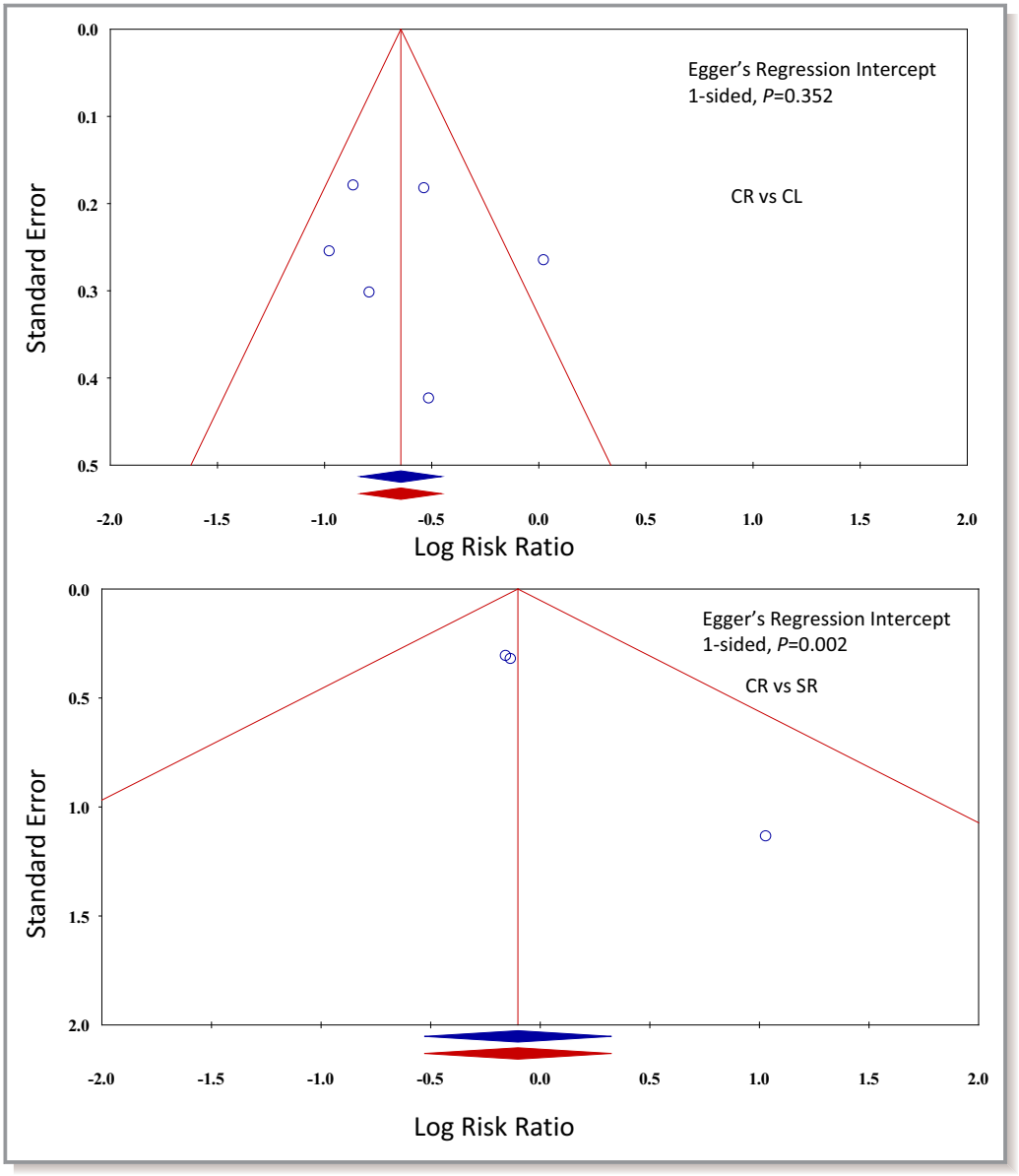

Figure 3. Depiction of publication bias for MACE for 2 strategies. Hollow blue circles represent available studies. Hollow red circles represent imputed studies. The solid blue diamond is the log risk ratio for MACE prior to publication bias adjustment. The solid red diamond is the log risk ratio for MACE after publication bias adjustment. CL indicates culprit lesion revascularization; CR, complete revascularization; MACE, major adverse cardiovascular events; SR, staged revascularization.

multivessel disease. We attempted to minimize this variation by using a uniform definition of MACE (Table S2) for all RCTs, but this still may have contributed to the heterogeneity observed. Other limitations included limited availability of procedural and index hospitalization details from the studies included in the analysis, thus we have not assessed procedural risks, length of hospitalization, or financial implications of CR and SR compared with each other and with CL. Another limitation of these meta-analyses is the lack of patient-level data, and that prevented us from performing covariate-adjusted or time-to-event analysis. Lastly, we were not able to evaluate the impact of chronic total occlusions and complex bifurcation lesions in nonculprit territory due to the lack of reporting in published studies. This is an area that warrants future investigation.

Conclusions

The findings from our comprehensive meta-analyses suggest that current practice guidelines indicating evidence of harm with CR as a strategy for revascularization for nonculprit vessels may need to be reassessed. A large ongoing RCT,

COMPLETE (NCT01740479)[44] would help clarify the role of CR in patients presenting with STEMI undergoing PCI of the culprit lesion. Nevertheless, until results from additional RCTs are available to guide decision making in such scenarios, clinical judgment should prevail in treating patients with multivessel coronary artery disease presenting with STEMI.

Disclosures

None.

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