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PII: S0002-9149(24)00857-9
DOI: https://doi.org/10.1016/j.amjcard.2024.12.013
Reference: AJC 27886

To appear in: *The American Journal of Cardiology*

Received date: 20 August 2024
Revised date: 8 November 2024
Accepted date: 3 December 2024

Please cite this article as: Abdulrahman M. Almizel MD , Jeremy Y. Levett MD , Tetiana Zolotarova MD , Mark J. Eisenberg MD MPH , Meta-analysis comparing immediate versus staged complete revascularization for ST-elevation myocardial infarction with multivessel disease, *The American Journal of Cardiology* (2024), doi: https://doi.org/10.1016/j.amjcard.2024.12.013

Meta-analysis comparing immediate versus staged complete revascularization for ST-elevation myocardial infarction with multivessel disease

Running title: Immediate versus Staged Complete Revascularization in STEMI

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Total word count: 2,769

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STRUCTURED ABSTRACT

Patients with ST-segment elevation myocardial infarction (STEMI) frequently present with multivessel coronary artery disease (CAD) during primary percutaneous coronary intervention (PCI), and the optimal timing of complete revascularization (CR) in these cases remains uncertain. This study aims to assess major adverse cardiovascular events (MACE) and procedural complications in STEMI patients with multivessel CAD undergoing immediate (index procedure) versus staged CR. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing immediate to staged complete revascularization (CR) in STEMI and multivessel CAD. Trials were identified via a systematic search of MEDLINE, Embase, and Cochrane Libraries from database inception to March 6, 2024. The data were analyzed using RevMan software. Five RCTs (n=1,415) were included in our study, which showed no significant differences in MACE (13.3% vs. 9.8%; RR: 1.07, 95% CI [0.62, 1.83]), all-cause mortality (3% vs. 4.55%; RR: 0.70, 95% CI [0.41, 1.21]), or myocardial infarction (4.5% vs. 2.6%; RR: 1.43, 95% CI [0.58, 3.55]) at a weighted mean follow-up duration of 16 months. However, the staged group had a higher rate of unplanned revascularization (8.6% vs. 4.4%; RR: 1.92, 95% CI [1.21, 3.04]). In conclusion, in STEMI patients with multivessel CAD, at a mean follow-up of approximately 1.3 years, there is no significant difference in immediate versus staged revascularization for MACE; however, staged revascularization was associated with a significantly higher incidence of unplanned ischemia-driven revascularization. Staged revascularization within the index hospitalization may be as effective as immediate complete revascularization; further trials are needed to confirm this.

CONDENSED ABSTRACT

We conducted a meta-analysis of 5 randomized controlled trials comparing immediate to staged CR in STEMI patients with multivessel CAD. There was no significant difference in major adverse cardiovascular events, all-cause mortality, and myocardial infarction rates between immediate and staged complete revascularization. However, staged revascularization was associated with a higher incidence of unplanned ischemia-driven revascularization.

Key Words: Complete revascularization, culprit-lesion, percutaneous coronary intervention, multivessel disease, ST-segment elevation myocardial infarction, meta-analysis.

ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
CAD	Coronary Artery Disease
FFR	Fractional Flow Reserve
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
AKI	Acute Kidney Injury
PCI	Percutaneous Coronary Intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
STEMI	ST-Segment Elevation Myocardial Infarction
TVR	Target Vessel Revascularization
TLR	Target Lesion Revascularization

CR Complete Revascularization

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the optimal reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI). A significant proportion of patients presenting with STEMI also present with multivessel coronary artery disease (CAD), which is associated with a significantly increased risk of adverse clinical outcomes.[1,2] Previous meta-analyses have highlighted the association of complete revascularization (CR) with reduced cardiovascular mortality in STEMI patients with multivessel CAD without cardiogenic shock.[3,4] The American College of Cardiology (ACC)/American Heart Association (AHA) 2021 and European Society of Cardiology (ESC) 2023 guidelines advocate for CR in hemodynamically stable patients with STEMI and multivessel disease.[5,6] However, these guidelines do not provide specific recommendations regarding the timing of revascularization. Recent large trials, such as the MULTISTARS AMI, have directly compared immediate to staged CR.[7,8] Their findings suggest that immediate multivessel PCI is noninferior to staged PCI, which challenges earlier findings from smaller studies and observational research.[9,10] This meta-analysis evaluates major adverse cardiovascular events (MACE) and procedural complications in STEMI patients with multivessel CAD randomized to immediate versus staged CR.

METHODS

We conducted our systematic review and meta-analysis according to a predefined protocol, adhering to the reporting guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[11] The protocol was publicly preregistered on the Open Science Framework on March 6, 2024.[12] Ethical approval was not required as per the TriCouncil Policy Statement (2022), article 2.2, which exempts research that relies

exclusively on publicly available information.

Data Sources and Search Strategy

We systematically searched MEDLINE via PubMed, Embase via Ovid, and the Cochrane CENTRAL (Central Register of Controlled Trials) databases from their inception through March 6, 2024. Our search terms included keywords from titles and abstracts, as well as Medical Subject Headings (MeSH) related to multivessel, STEMI, PCI, and RCT. The search details are provided in Supplementary Appendix A. We also reviewed reference lists of included trials and checked clinicaltrials.gov to identify ongoing trials. To focus specifically on clinical trials, we utilized the Cochrane Collaboration's search filter to restrict our search results.[13]

Study Selection

The studies identified in our systematic search were imported into Covidence, where duplicate citations were systematically removed.[14] Subsequently, 2 reviewers, A.M.A.and T.Z., screened titles and abstracts using predetermined inclusion and exclusion criteria. Eligible citations were retrieved for full-text review. Disagreements were resolved through consensus or with a 3rd reviewer (J.Y.L.). Included studies were RCTs comparing immediate versus staged CR in patients with STEMI and multivessel CAD. Immediate CR was defined as revascularization of the non-culprit vessel during the index PCI, while staged CR referred to revascularization performed later, either during the same hospital admission or as an outpatient procedure. Each study had to report at least 1 predefined primary endpoint (listed below), with a minimum follow-up duration of 1 year. Exclusion criteria involved studies with more than 10% of patients in cardiogenic shock, as well as reviews, editorials, and crossover studies. Selected trials were required to be published in either French or English.

Data Extraction

Two reviewers independently conducted data extraction using a pre-tested form within Covidence. Discrepancies were resolved through consensus or by 3rd reviewer if necessary (J.Y.L.). Extracted data included study characteristics, procedural details, and baseline patient characteristics. Our primary outcome was MACE, as defined by each of the included studies. These primary outcomes were assessed at a follow-up duration of ≥1 year. Additionally, data for secondary outcomes were collected at ≥1 year, including all-cause mortality, cardiovascular mortality, myocardial infarction (MI), unplanned ischemia-driven revascularization, stent thrombosis, target vessel/lesion revascularization (TVR/TLR) as defined by the included studies, re-hospitalization, stroke, and acute kidney injury (AKI).

Quality Assessment and Statistical Analysis

The risk of bias for included RCTs was assessed using the Cochrane Risk of Bias (RoB 2) tool, and independently evaluated by 2 reviewers, with disagreements resolved by consensus or a 3rd reviewer (J.Y.L.).[15] All eligible studies were included in the manuscript, regardless of study quality. The main summary measures were relative risks (RR) and 95% confidence intervals (CIs). Data synthesis and meta-analysis were conducted using DerSimonian and Laird random-effects meta-analytic models with inverse variance weighting. All analyses were performed using RevMan (The Cochrane Collaboration).[15] For heterogeneity assessment, the amount of between-study variability was estimated using the I^2 statistic.

RESULTS

Search Results

Following a systematic search, 1,890 citations were retrieved, of which 1,264 remained after removal of duplicates (Figure 1). Among these, 51 full-text articles were assessed for

eligibility, with 5 RCTs meeting our inclusion criteria.[8,9,16-18]

Study and Procedural Characteristics

Our meta-analysis included 5 RCTs totaling 1,415 participants (703 randomized to immediate CR and 712 to staged CR), with a weighted mean follow-up duration of 15.6 months (Table 1). Studies were published between 2009 and 2023. In the staged CR arm, the timing of the staged procedure ranged between 2.5 to 56 days post-primary PCI. Notably, 2 of the studies utilized fractional flow reserve (FFR)-guided technology for complete revascularization, while the remaining 3 used an angiographically-guided approach.

Baseline Clinical and Demographic Characteristics

Male individuals constituted most of the sample, ranging from 62.3% to 80.8% (Table 2), with ages varying between 58.6 to 66 years. Patient characteristics were generally well balanced. The prevalence of diabetes mellitus (DM) ranged from 13.8% to 40.7%, and hypertension was noted in 40% to 94% of patients. All patients included in the study presented with STEMI. The incidence of prior MI among these patients ranged from 0.9% to 14.9%.

Quality Assessment

The overall RoB 2 across included trials was low (Supplementary Appendix C). All domains demonstrated low risk of bias except for the MULTISTAR AMI Trial (n= 840). This trial raised "some concerns" in the domain of deviation from the intended intervention, particularly evidenced by a crossover rate of up to 2.9% from the immediate CR group to the staged CR group.

Major Adverse Cardiovascular Events

Staged CR was associated with a 13.3% incidence of MACE, compared to 9.8% in the immediate CR group, with a risk ratio (RR) of 1.07 and a 95% confidence interval (CI) of 0.62-

1.83 (Figure 2). All-cause mortality rates were 3% in the staged CR group and 4.55% in the immediate CR group, with an RR of 0.70 and a 95% CI of 0.41-1.21 (Figure 3). For cardiovascular mortality, rates were 1.8% and 2.7% in the staged and immediate CR groups, respectively, with a RR of 0.66 and a 95% CI of 0.32-1.39 (Figure 3). The incidence of MI was 4.5% in the staged CR group and 2.6% in the immediate CR group, with a RR of 1.43 and a 95% CI of 0.58-3.55 (Figure 3). Notably, unplanned ischemia-driven revascularization was higher in the staged CR group at 8.6% compared to 4.4% in the immediate CR group, with an RR of 1.92 and a 95% CI of 1.21-3.04 (Figure 3). The incidence of rehospitalization was not pooled due to limited data availability, as it was reported in only 2 trials. Rehospitalization rates attributable to heart failure did not show a significant difference in the MULTISTAR Trial (SR: 1.4% vs. IR: 1.2%). [8] Similarly, there was no significant difference in rehospitalization rates between groups the Politi trial (SR: 13.8% vs. IR: 12.3%). [17]

Procedural Complications

The incidence of AKI was low across both intervention groups, ranging from 1.5% to 3.6% in the immediate CR group and 2.9% to 3.1% in the staged CR group (Table 4). Pooling of the incidences was not performed as data were only reported in 2 trials. We did not observe any statistically significant difference in the incidence of stent thrombosis (SR:1.5% vs IR:1.8%; RR: 0.81, 95% CI [0.33, 1.98]; Figure 3).

DISCUSSION

This study was designed to compare major adverse cardiovascular and safety outcomes between immediate CR and staged CR in STEMI patients with multivessel disease. We found no significant difference in MACE, all-cause mortality, or MI. However, the incidence of unplanned ischemia-driven revascularization was significantly higher in the staged CR group.

Previous meta-analyses have shown that CR is associated with a reduction in

cardiovascular mortality in patients with STEMI and multivessel CAD without cardiogenic shock.[3,4] Multiple meta-analyses have compared immediate and staged CR in patients with ACS, showing reduced rates of recurrent MI and unplanned revascularization with immediate revascularization, while finding no significant differences in all-cause mortality or MACE.[19,20] To the best of our knowledge, our meta-analysis is the first to focus exclusively on STEMI patients and to include newly published trials, such as the MULTISTARS AMI trial.[8]

The optimal timing for CR in hemodynamically stable STEMI patients with multivessel disease remains uncertain. The ESC 2023 guidelines recommend complete revascularization either during the index PCI or within 45 days.[6] Similarly, the ACC/AHA 2021 guidelines recommend CR, typically using a staged approach after successful primary PCI, though immediate CR may be considered in selected cases with low-complexity multivessel disease.[5]

In the absence of clear timing guidelines, interventional cardiologists frequently choose a staged PCI strategy for STEMI patients with multivessel CAD. This choice is influenced by concerns about potential immediate intervention risks, as well as the logistical and human factors associated with achieving complete revascularization during primary PCI. These risks include contrast-induced nephropathy, excessive contrast use, and acute-phase complications like arrhythmias and prothrombotic states.[21-23] Furthermore, logistical challenges, potential fatigue, and extended procedure durations often further influence decision-making towards staged CR.

Recent trials have provided further insights into the optimal timing of revascularization in patients with STEMI and multivessel disease. The MULTISTARS AMI trial demonstrated that immediate PCI significantly reduced MACE compared to staged PCI in STEMI patients.[8] However, the BIOVASC trial found no significant difference in MACE between immediate and staged CR in ACS patients.[7] In line with this, the COUCA trial, a prematurely discontinued and

underpowered randomized controlled trial, found no significant difference in MACE between immediate and staged CR.[16] Furthermore, immediate intervention was linked to higher overall mortality.[16]

While our analysis showed no significant differences in MACE, all-cause mortality, cardiovascular mortality, or recurrent myocardial infarction (MI), we observed a significant increase in the incidence of unplanned ischemia-driven revascularization in the staged CR group. This trend appears to be influenced by data from the larger MULTISTARS AMI trial whereby the timing of the staged procedure was notably distant from the index procedure, with a median delay of 32 days.[8] Outcomes from the optical coherence tomography sub-study of the COMPLETE trial revealed that approximately half of obstructive non-culprit lesions are associated with unstable plaque morphology.[24] This prolonged interval between the index event and revascularization may have contributed to the observed increase in unplanned ischemia-driven revascularization events within the staged group.

In the MULTISTARS AMI trial, the outcomes for immediate versus staged revascularization were similar when the staged procedure was performed within 10 days of the index PCI. However, after 10 days, the curve diverged, with the staged intervention showing higher incidence rates of adverse outcomes.[8] This highlights the critical role that timing plays in optimizing patient outcomes following staged revascularization. As shown in Figure 4, which is adapted from the MULTISTARS AMI trial, these findings reinforce the need for careful consideration of the timing of staged procedures to avoid delays that may lead to worse outcomes.[8]

The extent of vessel involvement may impact outcomes following complete revascularization. Kakar et al., in a BIOVASC substudy, suggest that immediate

revascularization may reduce myocardial infarction risk in patients with three-vessel disease but shows no significant benefit for those with two-vessel disease.[25]

Although it is believed that delaying non-culprit PCI may be beneficial in reducing the incidence of AKI, we found no significant difference in AKI between immediate and staged revascularization strategies. While a recent meta-analysis indicated a reduced total contrast volume is associated with immediate revascularization,[20] patient-specific factors including baseline renal function, ejection fraction, and the timing of contrast administration are likely more important than the total contrast volume.

Our meta-analysis has several potential limitations. First, there was substantial variability in the timing of staged CR across studies, with intervals ranging from 2.5 to 56 days, which may have influenced outcomes in the staged CR arm. Second, inconsistencies in the definition of MACE among trials could lead to either underestimation or overestimation of the incidence of MACE. However, secondary endpoints remained consistent across trials. Additionally, the results of the meta-analysis may be significantly influenced by the data from the MULTISTARS AMI trial, which constitutes a large portion of the total sample size, introducing potential bias.[8] Finally, the sample size was insufficient for several endpoints, highlighting the need for further studies to adequately address this question. Despite some observed benefits of immediate revascularization, current evidence does not allow for definitive conclusions. Nevertheless, this meta-analysis offers an updated and STEMI-specific review, underscoring its relevance and specificity to this patient population, and helping guide treatment decisions while waiting for further trials.

CONCLUSION

Our study compared cardiovascular outcomes between immediate and staged complete

revascularization in patients with STEMI and multivessel CAD. Staged CR showed comparable outcomes to immediate CR, albeit with a higher incidence of unplanned ischemia-driven revascularization. Early staged revascularization may result in outcomes comparable to immediate revascularization, supporting the safety and efficacy of early staged procedures. Future randomized studies that assess the timing of staged procedures could offer valuable insights in guiding the management of patients with STEMI and multivessel disease.

Acknowledgements

Abstract illustration was generated from adapted figures provided by Servier Medical Art (https://smart.servier.com/), licensed under a Creative Commons Attribution 4.0 Unported License.

DISCLOSURES

Author Contributions: M.J.E. was the senior author for the study. M.J.E. and A.M.A. had full access to all the data in the study and take responsibility for the integrity and accuracy of the data analysis.

Concept and design: A.M.A., J.Y.L., T.Z., M.J.E.

Acquisition, analysis, or interpretation of data: A.M.A., J.Y.L., T.Z., M.J.E.

Drafting of the manuscript: A.M.A.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: J.Y.L.

Administrative, technical, or material support: M.J.E., T.Z.

Supervision: J.Y.L., T.Z., M.J.E.

All authors have made substantial contributions to this study and agreed to publish this data.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercials, or not-for-profit sectors.

Competing interests

None.

HIGHLIGHTS

- Patients with STEMI often present with multivessel CAD. The optimal timing for complete revascularization during primary PCI remains uncertain.
- Our review and meta-analysis found no significant differences in MACE, all-cause mortality, or MI between immediate and staged complete revascularization. However, staged complete revascularization had a higher rate of unplanned revascularization.
- Future randomized studies on the timing of staged procedures could offer valuable insights for managing STEMI patients with multivessel disease.

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FIGURE LEGENDS

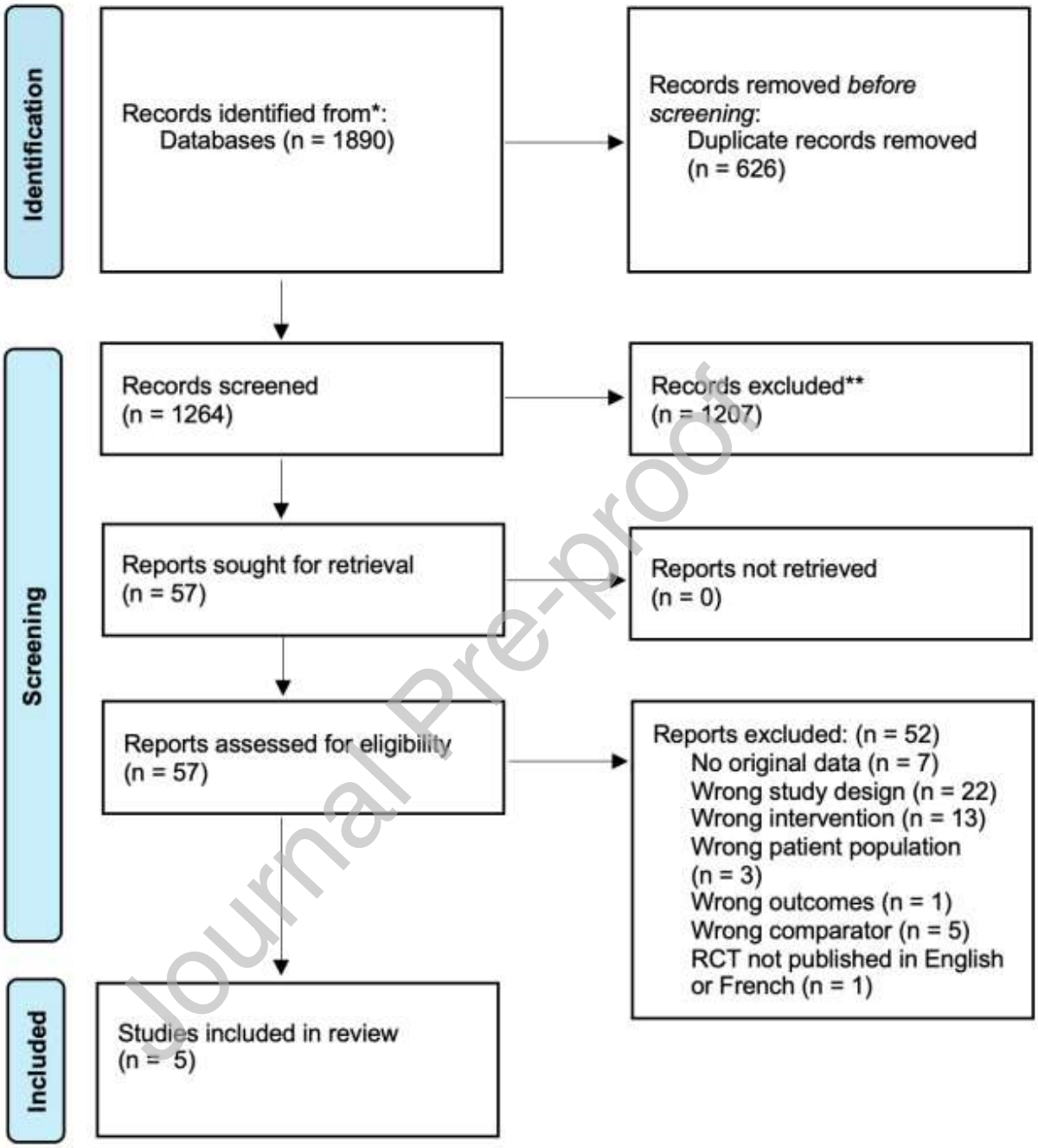

Figure 1. PRISMA flow diagram of study selection.

Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = Randomized Controlled Trial.

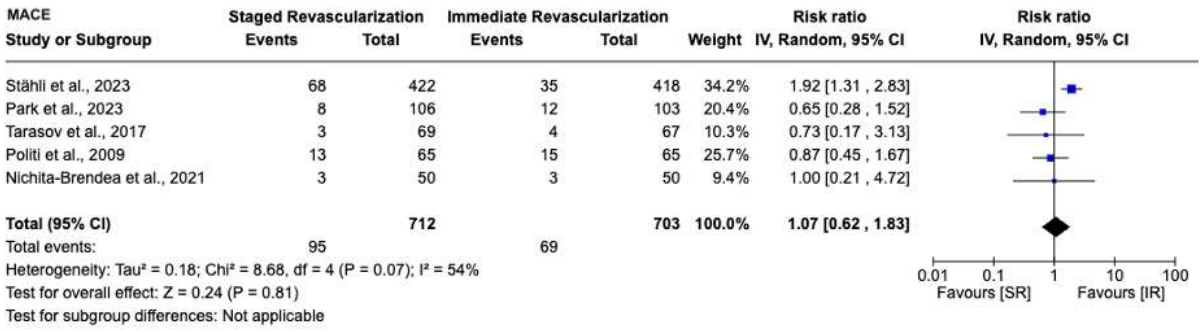

Figure 2. Forest plot of the risk ratio of MACE at 12 months or more in STEMI patients with multivessel disease randomized to immediate versus staged complete revascularization.

Abbreviations: CI = Confidence Interval; IR = Immediate Revascularization; MACE = Major Adverse Cardiovascular Events; SR = Staged Revascularization.

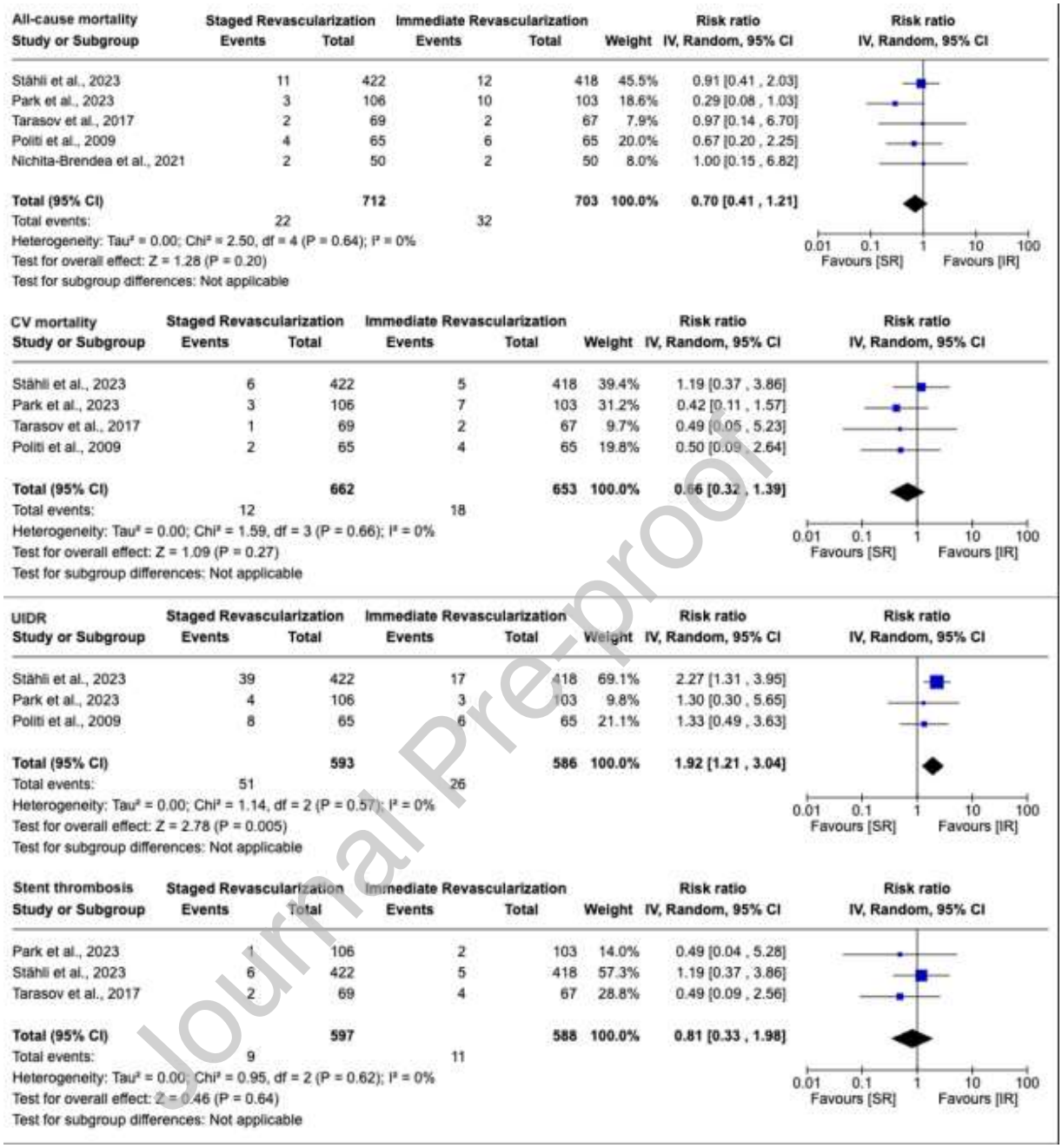

Figure 3. Forest plot of the relative risks of major cardiovascular outcomes in STEMI patients with multivessel disease randomized to immediate versus staged complete revascularization.

Abbreviations: CI = Confidence Interval; CV = Cardiovascular; IR = Immediate Revascularization; RR = Relative Risk; SR = Staged Revascularization; UIDR =

Unplanned Ischemia-Driven Revascularization.

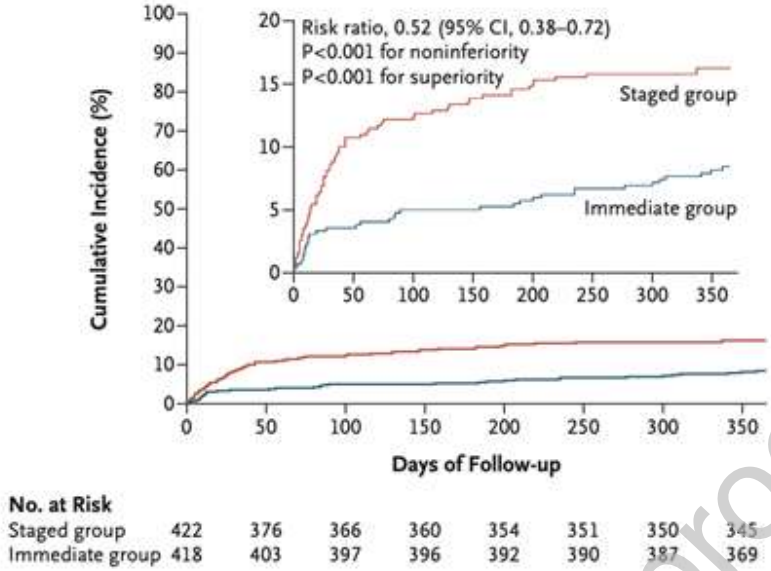

Figure 4. Cumulative incidence of primary endpoints at 1 year in STEMI patients with multivessel disease, randomized to immediate versus staged complete revascularization. Reproduced with permission from Stähli BE, et al. Timing of Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med. 2023;389(15):1368-1379. © Massachusetts Medical Society.

Table 1: Study Characteristics of Immediate versus Staged Complete Revascularization Trials in Patients with ST-Elevation Myocardial Infarction and Multivessel Disease

	Sample Size (n)	Countries of Enrollment	Maximum Follow-Up, mo	PCI Strategies subgroup numbers		Time from Randomization to Complete Revascularization Procedure (days) in the staged arm	Study Population	FFR Measurements Obtained
				IR	SR			
Stähli (2023)	840	MULTINATIONAL	12	418	422	32	STEMI	YES*
Park (2023)	209	KOREA	12	103	106	4.4	STEMI	NO†
Nichita-Brendea (2021)	100	ROMANIA	12	50	50	2.5	STEMI	YES
Tarasov (2017)	136	RUSSIA	12	67	69	10.1	STEMI	NO
Politi (2009)‡	214	ITALY	30§	65	65	56	STEMI	NO

Abbreviations: FFR=Fractional Flow Reserve; IR=Immediate revascularization; MO=Month; NR=Not Reported; PCI=Percutaneous Coronary Intervention; SR=Staged revascularization; STEMI=ST-Segment Elevation Myocardial Infarction.

* FFR measurements obtained in 2.9% of the IR arm vs 9.3% of the SR arm.

† FFR measurements obtained in 10% of the IR arm vs 12% of the SR arm.

‡ This was a. A 3-arm trial total of 130 participants were randomized between IR and SR. A total of 218 were randomized to the trial between SS, MS, and culprit-only revascularization.

§ Mean follow-up, mo.

Table 2: Baseline Demographic and Clinical Characteristics of Immediate versus Staged Complete Revascularization Trials in Patients with ST-Elevation Myocardial Infarction and Multivessel Disease

	Age (mean/median)		Male (%)		DM (%)		HTN (%)		Current Smoker (%)		STEMI (%)		Prior					
	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR	MI (%)		PCI (%)		Stroke (%)	
													IR	SR	IR	SR	IR	SR
Stähli (2023)	66	64	76.8	80.8	15.8	15.4	54.5	50.2	33.9	35.4	100	100	6.7	4.8	7.9	5.5	1.7	2.6
Park (2023)	63.3	62.2	79.6	83	40.7	34.9	54.3	45.2	36.8	41.5	100	100	0.9	0.9	1.9	0	NR	NR
Nichita-Brendea (2021)	NR	NR	74	72	24	22	40	48	50	42	100	100	NR	NR	NR	NR	NR	NR
Tarasov (2017)	58.6	59.1	71.6	62.3	23.9	20.3	94	88.4	NR	NR	100	100	14.9	5.8	NR	NR	0	2.9
Politi (2009)	64.5	64.1	76.9	80	13.8	18.5	49.2	64.6	NR	NR	100	100	NR	NR	NR	NR	NR	NR

Abbreviations: DM=Diabetes Mellitus; HTN=Hypertension; IR=Immediate Revascularization; MI=Myocardial Infarction; NR=Not Reported; PCI=Percutaneous Coronary Intervention; SR=Staged Revascularization; STEMI=ST-Segment Elevation Myocardial Infarction.

Table 3: Major Adverse Cardiovascular Evemts at 12 Months or More of Immediate versus Staged Complete Revascularization Trials in Patients with ST-Elevation Myocardial Infarction and Multivessel Disease

	Sample Size (n)		All-Cause Mortality, n (%)		Cardiovascular Mortality, n (%)		MACE, n (%)		Repeat Myocardial Infarction, n (%)		UIDR, n (%)	
	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR
Stähli (2023)	418	422	12 (2.9)	11 (2.6)	5 (1.2)	6 (1.4)	35 (8.5)	68 (16.3)	8 (2)	22 (5.3)	17 (4.1)	39 (9.3)

Park (2023)	103	106	10 (9.7)	3 (2.8)	7 (6.7)	3 (2.8)	12 (11.6)	8 (7.5)	2 (1.9)	2 (1.8)	3 (2.9)	4 (3.7)
Nichita-Brendea (2021)	50	50	2 (4)	2 (4)	NR	NR	3 (6)	3 (6)	NR	NR	NR	NR
Tarasov (2017)	67	69	2 (3)	2 (2.9)	2 (3)	1 (1.4)	4 (5.9)	3 (4.3)	5 (7.5)	2 (2.9)	2 (3)	1 (1.4)
Politi (2009) [l]	65	65	6 (9.2)	4 (6.2)	4 (6.3)	2 (3.1)	15 (23.1)	13 (20)	2 (3.1)	4 (6.2)	6 (9.2)	8 (12.3)

Abbreviations: IR=Immediate Revascularization; MACE=Major Adverse Cardiovascular Event; NR=Not Reported; SR=Staged revascularization; STEMI=ST-Segment Elevation Myocardial Infarction; UIDR=Unplanned ischemia-driven revascularization.

Declaration of Interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: