# SYSTEMATIC REVIEW

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# Comparison of immediate and staged complete revascularization in patients with acute coronary syndrome and multivessel coronary disease: a systematic review and meta-analysis

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# Abstract

**Background** The optimal timing of complete revascularization (CR) in patients with acute coronary syndrome (ACS) and multivessel disease (MVD) is still debated. The safety and efficacy of immediate and staged CR (ICR vs. SCR) in this patient group were thus compared.

**Methods and results** PubMed, Embase, and CENTRAL were systematically searched to identify randomized controlled trials of CR strategies for MVD. Studies comparing cardiovascular benefits between ICR and SCR in ACS patients with MVD were included. Short- and long-term outcomes were compared using random-effect risk ratios (RRs). The analysis included seven studies with 3445 patients. The ICR and SCR groups showed comparable risks of all-cause death at 1 year (RR: 1.18; 95% CI: 0.72 to 1.95), but the risk increased at 1 month in ICR patients (RR: 2.35; 95% CI: 1.12 to 4.91). ICR reduced the risk of myocardial infarction (MI, RR: 0.54; 95% CI: 0.33 to 0.90) and target vessel revascularization (TVR, RR: 0.62; 95% CI: 0.45 to 0.85) at 1 year.

**Conclusion** The all-cause death rates were comparable between ICR and SCR strategies. CR at index procedure could reduce MI and TVR rates at 1 year (46% and 38%, respectively). Future studies need to obtain more precise evidence and identify the cardiovascular benefits of these two strategies.

# Clinical trial number Not applicable.

**Keywords** Acute coronary syndrome, Multivessel disease, Immediate complete revascularization, Staged complete revascularization, Percutaneous coronary intervention

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## Introduction

Multivessel disease (MVD) was reported in more than half of patients with ST- and non-ST-segment elevation myocardial infarction (STEMI and NSTEMI), which is foreboding poorer cardiovascular prognosis than the single-vessel disease [1, 2]. The 2023 guidelines of the European Society of Cardiology strongly recommend (Class 1a) complete revascularization (CR) for managing MVD in hemodynamically stable STEMI patients within 45 days, or more aggressively, at index percutaneous coronary intervention (PCI) procedure [3]. Theoretically, CR could minimize the burden of residual ischemia risk, reduce future major cardiovascular events, and improve the prognosis of acute coronary syndrome (ACS) patients with MVD [4, 5]. Accumulating evidence also suggests CR as the preferred strategy for survival and symptomatic benefits in STEMI and NSTEMI patients [6, 7]. Compared with immediate CR (ICR), Staged CR (SCR) is associated with lower contrast use during the index procedure, but it exposes patients to multiple procedure which may increase the risk of non- and coronary artery complications [8]. Accordingly, discussions about the optimal timing of CR have become an inevitable and crucial topic in treating ischemic heart disease. However, the optimal CR strategy is inconclusive at present.

Although previous studies have compared cardiovascular benefits in MVD patients after ICR and SCR (where ICR involves CR of all lesions at index procedure and SCR comprises initial CR of the culprit lesion before addressing non-culprit lesions), most of the generated evidence is based on observational studies with lower evidence grade [9]. The conclusion was controversial with recently randomized controlled trial (RCT)-based meta-analyses, which investigated differences between ICR and SCR [10, 11]. However, the studies by Bujak et al. did not focus on outcomes with different time points, as well as the conclusion on the short-term prognosis in the study by Cheema et al. was based on limited studies., which restricts the generalization of these conclusions. Accordingly, the prognoses in different follow-up periods between ICR and SCR are still unclear [10–12]. Herein, we performed a meta-analysis on the latest RCTs to compare the safety and efficacy of ICR and SCR in ACS patients with MVD.

#### Method

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement (Supplementary Material 3) [13]. A prespecified protocol has been registered in INPLASY with the record number INPLASY202380112 and followed for all steps. PubMed, Embase, and CENTRAL were searched on 28 August 2023 using the combination of the following keywords: "multivessel disease," "staged revascularization," "immediate revascularization," and "acute coronary syndrome." The search was updated on 11 October 2023 (Supplementary Material 4). Reference lists of previous pertinent published literature were manually investigated for potential studies along with two gray literature databases (Open Gray and The Nation Technical Information Service).

#### Study selection

RCTs were included without language restriction, wherein recruited individuals with MVD undergoing emergency PCI were randomized to ICR or SCR. ICR was defined as revascularization at index procedure of both the culprit and non-culprit arteries. SCR was considered the initial treatment of culprit lesion only at PCI, followed by single or multiple revascularizations of all non-culprit lesions at index hospitalization or a few weeks post-discharge.

Studies including patients who had suffered from cardiogenic shock were excluded. Further, trials without at least one outcome of interest were eliminated. Studies with the most extended duration or comprehensive information for the same trials were included in the analysis.

Identified titles and abstracts were screened, based on prespecified criteria, by two reviewers (Xuan-Yan Liu and Jing-Chao Sun), and any discrepancies were resolved by a third reviewer. Any study classified as "potentially relevant" was full-text screened.

#### Data abstraction

Two authors (Xian-Dan Wu and Xian Lin) independently and systematically conducted data extraction using a predesigned data collection sheet. Disagreements were settled by consensus or by the decision of another investigator (Bin-Hua Ye) when and as necessary. Extracted data included first author, publication year, country, sample size, study design, demographic characteristics (sex and age), mean follow-up duration, types of ACS, left ventricular ejection fraction (LVEF), procedural characteristics (numbers of treated vessels per patient, procedure time, stents per patient, time to staged procedure and procedure contrast use during the index plus stage procedure), primary and secondary outcomes of interest.

#### Outcomes

The primary outcomes were the incidence of all-cause death at 1 month and 1 year. Secondary outcomes included MI, stroke, bleed events, target vessel revascularization (TVR), and the combination of all-cause death, MI, TVR, and stroke at 1 month and 1 year after the index procedure. The definitions of extracted secondary outcomes across studies were consistent. The definition of MI was based on the Third Universal Definition of Myocardial Infarction [14]. TVR was considered any repeated PCI or bypass surgery of the initially treated vessel segment. Stroke included ischemic and hemorrhagic strokes. Bleed events were evaluated based on the Bleeding Academic Research Consortium scale where any clinical, imaging, or laboratory indication of bleeding was considered as type 3 event and fatal bleeding was deemed as type 5 event [15].

#### **Bias and quality assessment**

Two reviewers (Yue-Lin and Yan-Yan Li) separately assessed the bias between studies using the revised Cochrane risk-of-bias tool (ROB2) in the following six domains: selection, performance, detection, attrition, reporting, and overall biases [16]. Randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result were used to classify the risk as low, some concern, or high. The quality of outcomes was categorized into very low, low, moderate, and high by The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [17]. The bias risk and quality of evidence were evaluated by two authors (Xuan-Yan Liu and Xian-Dan Wu), and all differences were settled by a third reviewer (Bin-Hua Ye).

## Statistical analysis

Analyses were conducted using STATA software version 17 (STATA Corporation, College Station, Texas). Summary estimate risk ratios (RRs) were determined using the DerSimonian and Laird random-effect model, with zero-event included in the calculation by a 0.5 continuity correction. An intention-to-treat analysis was used to analyze outcomes. The significance of two-sided P-values was assessed at an alpha level of 0.05. Variates expressed as median with interquartile range were transformed into mean and standard deviation [18, 19]. The I2 statistic quantified the degree of inter-study heterogeneity, and a sensitivity analysis with the leave-one-out method was used to identify studies displaying inappropriate effects [20]. To address any discrepancy that might be raised by the study design and patient characteristics, we divided studies into STEMI and NSTEMI subgroups to compare the two CR strategies in diverse infarct types because guidelines recommend different interventional strategies for these two groups of patients [3]. Subgroup analysis was also conducted through characteristics of trials and participants to elucidate the heterogeneity source. The Trim-and-Fill method visually assessed and corrected the funnel plot asymmetry attributable to publication bias [21]. Due to the possible increased risk of random error attributed to small sample size and repeated significant testing, trial sequential analysis (TSA) was conducted using Viewer version 0.9.5.10. beta (Copenhagen Trial Unit, Denmark) for evaluation of the credibility of statistical results [22].

# Results

# Search results

Our initial search yielded 1212 studies with 451 duplications. Of these, 78 studies were included in full-text assessment via screening of their titles and abstracts. Four studies only reported 3- or 6-month relevant outcomes and were not included [23–26]. Three trials comparing ICR and SCR were excluded, as they were not truly randomized [27–29]. The detailed search procedure is shown in the flow diagram (Supplemental Material 1).

#### **Study characteristics**

The final analysis was conducted on 3445 patients from seven RCTs [30–36]. Four studies were restricted to individuals with STEMI [31, 35, 36], and two trials were restricted to NSTEMI [32, 34]. One study recruited all patients with ACS [30]. In addition, five trials were conducted in Europe [30, 33–36] and two studies were from Asia [32] and Africa [31]. All studies excluded patients with cardiogenic shock. The sample size varied from 78 to 1525 patients.

The mean follow-up length was 1-2.5 years; most study participants were male (ranging from 66.9 to 87.8%). The mean age was 65.1 years old. Five studies had reported LVEF [31–34, 36], while two did not. The routine medical therapy (dual antiplatelet and statins) is comparable in five studies [30–32, 34, 35]; two other studies did not report the medical therapy [33, 36]. The data about the comparison between ICR and SCR were extracted in the study that compared three different revascularization strategies [33]. The general characteristics of all the studies are depicted in Table 1.

#### **Characteristics of procedures**

The mean number of treated vessels per patient was 2.2-3.0 between treatment arms, which was similar among all studies (Table 2). In reported studies, the mean number of stents per patient was also close between the ICR and SCR groups (from 2.3 to 3.0). The SCR group had longer procedure time and higher contrast volume [30, 35, 36]. Saedella and colleagues only reported the data for the first procedure time and contrast used. The interval between procedures in the SCR group ranged from 4.7 to 58.6 days.

## Risk of bias and quality assessment

Several concerns of bias risk were speculated with all studies on various domains based on the ROB2 tool (Supplemental Material 1). Three trials did not announce the randomization process and the way of allocation concealment [31, 33, 36]. Considering CR in the BIOVASC

Study	Country	ACS	Simple size	Mean age, y	Sex, male (%)	Follow-up period, y	LVEF, %
Politi, 2010	Italy	STEMI	130	64.4	102 (78.5)	2.5	45.3
Maamoun, 2011	Egypt	STEMI	78	54.4	72 (87.8)	1.0	45.3
Saedella, 2016	Italy	NSTEMI	527	72.5	416 (78.9)	1.0	50.0
Tarasov, 2017	Russia	STEMI	136	58.9	91 (66.9)	1.0	51.3
Diletti, 2023	Netherlands	NSTEMI, STEMI or UA	1525	65.4	1187 (77.8)	1.0	NR
Park, 2023	Korea	NSTEMI	209	62.7	170 (81.3)	1.0	51.4
Stähli, 2023	Switzerland	STEMI	840	65.0	662 (78.8)	1.0	NR

#### Table 1 The characteristics of included studies

Abbreviation: ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; NR, not reported; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina

Table 2	The	proced	ural c	haracterist	ics of i	nclud	ed stud	ies
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Study	Vessels T Patient	Vessels Treated Per Patient		Stents Per Patient		Гіme, min	Time Between Procedures in	Volume of Contrast Used	
	ICR	SCR	ICR	SCR	ICR	SCR	the SCR arm, d	ICR	SCR
Politi, 2010	NR	NR	NR	NR	NR	NR	58.6 (12.9)	NR	NR
Maamoun, 2011	2.2 (0.4)	2.3 (0.5)	2.3 (0.5)	2.4 (0.5)	NR	NR	Within 7	NR	NR
Saedella, 2016	2.4 (0.5)	2.3 (0.8)	3.0 (1.5)	3.0 (1.5)	NR	NR	4.8 (1.2)	NR	NR
Tarasov, 2017	2.5 (0.5)	2.5 (0.5)	2.6 (0.5)	2.7 (0.6)	NR	NR	10.1 (5.1)	313.8 (101.5)	353.6 (167.6)
Diletti, 2023	2.2 (0.4)	2.2 (0.4)	3.0 (1.5)	3.0 (1.5)	65.1 (27.5)	91.4 (41.6)	15.7 (17.8)	203.6 (81.7)	247.0 (104.0)
Park, 2023	2.2 (0.4)	2.2 (0.4)	2.6 (0.9)	2.6 (1.0)	NR	NR	4.7 (7.0)	NR	NR
Stähli, 2023	2.2 (0.4)	2.2 (0.4)	3.0 (1.5)	3.0 (1.5)	74.8 (26.0)	107.8 (43.2)	36.7 (9.7)	256.7 (90.0)	334.1 (113.9)

Abbreviation: ICR, immediate complete revascularization; SCR, staged complete revascularization; NR, not reported

trial, some patients with ACS and MVD deviated from the intended intervention, but these deviations were balanced between groups [30]. However, the deviations were imbalanced in the MULTISTARS AMI trial where crossover was observed in 12 patients from the staged group but none from the immediate group [35]. The assessment conducted using the GRADE framework deemed the quality to be moderate for six outcomes (all-cause death, MI, TVR, and stroke at 1 year; all-cause death and TVR at 1 month) and low for three outcomes (MI, stroke at 1 month and bleed), while two outcomes (composite outcome at 1 year and 1 month) were graded as very low level (Supplemental Material 2).

#### 1-year outcomes

ICR and SCR groups had a similar risk of 1-year allcause death (3.7% vs. 3.4%, RR: 1.18; 95% CI: 0.72 to 1.95; P=0.51; I<sup>2</sup>=32.14%, Fig. 1). The TSA showed that although the z-curve crossed below the futility boundaries, the accumulated information size failed to reach the expectation size, which indicates that more trials are warranted to explore the difference in 1-year all-cause death between ICR and SCR (Supplemental Material 1). The composite risk was lower at 1 year (10.0% vs. 14.1%, RR: 0.72; 95% CI: 0.52 to 1.01; P=0.06; I<sup>2</sup>=47.39%, Supplemental Material 1) but without statistical significance. This trend was entirely driven by the markedly lower risk of MI (2.2% vs. 4.3%, RR: 0.54; 95% CI: 0.33 to 0.90; *P*=0.02; I<sup>2</sup>=18.14%, Supplemental Material 1) and TVR (4.2% vs. 6.5%, RR: 0.62; 95% CI: 0.45 to 0.85; *P*<0.001; I<sup>2</sup>=0, Supplemental Material 1) in patients allocated to ICR. Further, a nonsignificant increase in the risk of stroke (1.3% vs. 1.1%, RR: 1.10; 95% CI: 0.56 to 2.16; *P*=0.77; I<sup>2</sup>=0, Supplemental Material 1) was noted in the ICR group. The bleeding incidence with CR strategies was comparable in the three trials (1.8% vs. 2.0%, RR: 0.97; 95% CI: 0.48 to 1.97; *P*=0.93; I<sup>2</sup>=25.5%, Supplemental Material 1). The outcomes analysis is summarized in Table 3.

Although the visual assessment seemed asymmetry, the Trim-and-Fill method was used by imputing three trials on the left, and the results were similar to the primary outcome (RR: 0.85; 95% CI: 0.50 to 1.44, Supplemental Material 1), indicating no evidence of publication bias. Leave-one-out analysis proved the outcome's robustness, as the 1-year all-cause death did not significantly differ upon sequential omission of trials (Supplemental Material 1).

#### 1-month outcomes

The pooled analysis revealed the association of CR during the ICR with a higher risk of 1-month all-cause death after the index procedure than that of SCR (1.9% vs. 0.8%, RR: 2.35; 95% CI: 1.12 to 4.91; P=0.02; I<sup>2</sup>=0, Fig. 2). We excluded a prematurely terminated study by Park et al., the result was nonsignificant (1.5% vs. 0.6%, RR: 2.15; 95%

	Treatr	nent	Cont	rol			RR		Weight
Study	Events	Total	Events	Total		W	rith 95%	6 CI	(%)
Politi, 2010	6	65	4	65		1.55	[0.42,	5.78]	11.15
Maamoun, 2011	2	42	1	36		1.75	[0.15,	20.14]	3.87
Saedella, 2016	17	264	29	263	- <b></b>	0.56	[0.30,	1.04]	27.35
Tarasov, 2017	2	67	2	69		1.03	[0.14,	7.54]	5.61
Diletti, 2023	14	764	9	761		1.56	[0.67,	3.63]	20.28
Park, 2023	10	103	3	106		3.69	[0.99,	13.82]	11.07
Stähli, 2023	12	418	11	422		1.10	[0.48,	2.53]	20.67
Overall					+	1.18	[0.72,	1.95]	100.00
Heterogeneity: $t^2 = 0$	$1.14, I^2 = 1$	32.14%	$H^2 = 1.4$	7					
Test of $q_i = q_j$ : Q(6)	= 8.84, P	= 0.18							
Test of $q = 0$ : $z = 0.6$	55, P = 0.2	51							
					1/4 1 4 16				

#### Random-effects model

Fig. 1 Risk of all-cause death in patients presenting with ACS without cardiogenic shock at 1 year

 Table 3 The results of the primary and second outcomes

Outcome	No. o	f Incidence Complete	e/ RR (95%CI)	Heterogeneity I <sup>2</sup> %	P value
	study	v Staged (%)			
1-year					
All-cause death	7	3.7/3.4	1.18 (0.72, 1.95)	32.14	0.51
Composite of all-cause death, MI, TVR, and stroke	5	10.0/14.1	0.72 (0.52, 1.01)	47.39	0.06
MI	6	2.2/4.3	0.54 (0.33, 0.90)	18.14	0.02
TVR	6	4.2/6.5	0.62 (0.45, 0.85)	0.00	< 0.001
Stroke	5	1.3/1.1	1.10 (0.56, 2.16)	0.00	0.77
1-month					
All-cause death	5	1.9/0.8	2.35 (1.12, 4.91)	0.00	0.02
Composite of all-cause death, MI, TVR, and stroke	3	3.1/4.8	1.02 (0.29, 3.60)	81.92	0.98
MI	4	0.8/2.1	0.41 (0.16, 1.07)	11.33	0.07
TVR	3	1.2/1.1	1.01 (0.31, 3.30)	0.00	0.99
Stroke	3	0.4/1.0	0.48 (0.17, 1.37)	0.00	0.17
Bleed	3	1.8/2.0	0.97 (0.48, 1.97)	25.50	0.93

Abbreviation: MI, myocardial infarction; TVR, target vessel revascularization; risk ratios

CI: 0.89 to 5.19; P=0.09;  $I^2=0$ ). Sensitivity analysis of the leave-one-out method indicated the study by Saedella et al. may introduce bias either (Supplemental Material 1). No difference was observed in MI, stroke, TVR, and the composite analysis (Supplemental Material 1). Table 3 shows the secondary outcome results.

#### Subgroup analyses

Subgroup analysis according to infarct type found that the 1-year all-cause death incidence was consistent among STEMI (RR: 1.23; 95% CI: 0.65 to 2.32, Supplemental Material 1) and NSTEMI patients (RR: 1.31; 95% CI: 0.46 to 3.71, Supplemental Material 1). We also conducted a subgroup analysis by interval time of SCR. The 1-year all-cause death of ICR against SCR was similar through diverse time-to-stage procedures (Supplemental Material 1). In addition, the subgroup analysis across the characteristics of trials and participants (regions, age, sample size and LVEF) produced similar conclusions to the primary outcome (Supplemental Material 1).

# Discussion

Herein, this meta-analysis of seven RCTs investigated and compared the survival improvement and cardiovascular benefits with two different revascularization strategies among ACS patients with MVD. There is no significant difference between ICR and SCR in 1-year all-cause death. Although heterogeneity exists in the

	Treatr	nent	Cont	trol		RR	Weight
Study	Events	Total	Events	Total		with 95%	CI (%)
Politi, 2010	2	65	0	65		— 5.16 [0.24, 1	09.55] 5.86
Saedella, 2016	6	264	2	263		3.03 [0.61,	15.18] 21.12
Tarasov, 2017	2	67	1	69		2.09 [0.19,	23.63] 9.31
Diletti, 2023	6	764	4	761		1.50 [0.42,	5.33] 33.96
Park, 2023	8	103	3	106		2.89 [0.75,	11.22] 29.76
Overall						2.35 [1.12,	4.91] 100.00
Heterogeneity: t <sup>2</sup>	= 0.00, I	$^{2} = 0.0$	0%, H <sup>2</sup> =	1.00			
Test of $q_i = q_j$ : Q(	(4) = 0.93	8, P = 0	.92				
Test of q = 0: z =	2.26, P	= 0.02					
					1/4 1 4 16 6	<del>,</del> 54	

# Random-effects model

Fig. 2 Risk of all-cause death in patients presenting with ACS without cardiogenic shock at 1 month

outcome, the leave-one-out analysis found a consistent result when studies were eliminated in sequence, as well as the subgroup analysis obtained similar outcomes. In the subgroup analysis conducted based on age, we found a higher all-cause death rate in patients < 65 years, which was contradictory to the cognize that younger is usually associated with a favorable prognosis. We assumed the opposite trends might be affected by a prematurely terminated study [32]. An adverse effect was observed in the ICR group on 1-month all-cause death. However, the result may be affected by the studies by Park et al. and Saedella et al. that while we excluded them respectively, the result became statistically nonsignificant. The risk of MI and TVR was lower among patients receiving ICR at 1 year but determined to be similar at 1 month. The occurrence of stroke and composite outcome, as well as the incidence of bleed, among the two strategies, were comparable at 1 year and 1 month. In addition, we found the functional assessment in the SCR group is applied more frequently. But we deemed that functional assessment could not affect the outcomes, as a network metaanalysis determined that functional assessment is not superior to angiography-guided CR in cardiovascular benefits [37].

The outcomes of the present meta-analysis were inconsistent with those of the previous observational trials, which demonstrated that SCR after the index procedure may be more beneficial to survival improvement among individuals with ACS and MVD [38, 39]. However, individuals in observational studies were primarily allocated by physicians based on the experience and characteristics of patients. Accordingly, patients with complex coronary lesions and (or) higher procedural complications incidence are more likely to receive SCR after the index procedure, which may introduce a relatively higher mortality risk [40]. Although the known confounders were controlled and propensity matching was used in both trials to balance the ICR and SCR groups, potential unmeasured confounders, such as patient comorbidities and discrepancies between lesion coronaries, could still exist. A previous pairwise and network meta-analysis that included 32 studies compared the three different CR strategies (ICR, SCR, or culprit-only) and revealed a trend toward ICR adverse effects on MVD during the index procedure [41]. As per the latest pooled result of non-randomized trials, ICR can impose a higher shortand long-term mortality risk [9]. However, according to the subgroup analysis of the trial by Vriesendorp et al., the increased 1-year all-cause death rates in the ICR group were driven by the results of studies including cardiogenic shock patients. As with any meta-analysis of observational data, bias assessment of enrolled nonrandomized studies, particularly immortal time bias, and publication bias, may restrict the interpretation of the pooled outcomes from observational studies [42].

In our study, the 1-year MI and TVR rates were similar to previous meta-analyses [11, 12, 43]. However, the perspective remains that prolonging the index procedure may increase the procedure-related events in the short term than SCR 48 h later [43]. We assume the reduction of MI and TVR rates mainly benefited from the spontaneous cardiac events decrease during the follow-up, not procedure-related, which could be associated with the rupture predisposition of unstable plaque and the subsequent coronary events in non-culprit lesions during SCR of the non-culprit vessel [44]. The high TVR rate in the SCR group seems parallel with a higher risk of target lesion revascularization, and a large proportion of these events occurred after CR [45], indicating that the SCR may not improve the incidence of revascularization by delaying operation.

We identified no statistical difference between ICR and SCR groups in the 1-year all-cause death and composite outcomes. The 1-year all-cause death risk observed herein was confirmed with previous meta-analyses of RCTs that showed similar rates for ICR and SCR [4, 9-12, 43]. However, one must exercise caution while interpreting the results because relative to a rare adverse event, these analyses were conducted on limited trials with insufficient participants, as well as the outcomes may affected by unmeasured confounders, especially in studies that did not reveal the details of randomization process even with balanced baseline characteristics. Although the present study included seven trials with 3445 patients, the TSA result showed that accumulated information size still did not exceed expectations, indicating a potential false-negatives result. We also found a higher absolute number of 1-year all-cause death in the ICR group, as well as in the majority of included studies. Thus, we assumed an increased tendency may appear with the expansion of sample size, and more trials are needed to enhance the credibility of the results.

Gaffar et al. proposed that patients allocated to ICR suffer a higher risk of 1-month all-cause death, but the events are little to pooling data among trials [9]. However, our meta-analysis found an inconsistent result with Gaffar et al. In addition, the subgroup analysis of a metaanalysis based on two RCTs showed a nonsignificant difference in 1-month all-cause death between ICR and SCR intervention [9]. The inconclusive results in these studies may be attributed to the bias from limited trials with small sample sizes.

These findings call upon future trials to identify the benefits of ICR and SCR on outcomes, including allcause death. Two ongoing trials, namely, TERMINAL, which compares ICR at the index procedure and SCR 30 days after initial hospitalization in STEMI-complicated MVD patients and Future Study, which compares fractional flow reserve (FFR)-guided ICR at index procedure versus FFR-guided SCR strategy, will elucidate the benefits of different strategies of CR on clinical outcomes and the importance of intracoronary functional evaluation in these settings.

#### Limitations

Several limitations should be considered in our metaanalysis. First, our result should be interpreted with caution because the TSA result of 1-year all-cause death between ICR and SCR was not statistically different, but the accumulated information seems inadequate, which may lead to false negatives. The two ongoing trials (TERMINAL and Future Study) about the different CR strategies could enhance the reliability of our conclusion in the immediate future. Second, the increasing morbidity of NSTEMI complicated MVD and the similar long-term prognosis between types of infarcts make it imperative to investigate the optimal strategy of CR for NSTEMI with MVD [46]. Our subgroup analysis based on infarct types suggested no significant difference between STEMI and NSTEMI, which may help in decision-making for operators in clinical practice while dealing with NSTEMI-complicated MVD. However, the robustness of the conclusion could be impaired because only two trials were pertinent to NSTEMI. In addition, the ROB2 tool showed some concern in some studies [31, 33, 36] and high risk in the MULTISTARS AMI trial. The risk of bias may favor the ICR because participants with complex coronary lesions tend to be allocated to the SCR group. But the baseline characteristics are similar between groups except in the study by Politi et al., in which patients with three-vessel disease are higher in the SCR group. Our sensitivity analysis showed a robust outcome, while the leave-one-out analysis found a similar result when the studies were excluded in sequence. Fourth, the generalizability of the results should be restricted to males because most recruited patients in trials were male despite subgroup analyses being conducted according to regions and other demographic characteristics of the study populations and finding similar results. Fifth, the conclusion of our meta-analysis was based on data in which female takes a limited proportion. Epidemiological data suggested that both younger and older women with STEMI suffered a higher risk of mortality than males [47, 48]. Unfortunately, we could not perform a subgroup analysis of sex without individual data. Finally, patients with coronary heart disease were recommended to be stratified by risk factors for the convenience of secondary prevention guidance [49]. We could not compare the benefits of ICR and SCR in different risk stratification patients owing to the absence of individual data.

# Conclusion

Current evidence from RCTs demonstrates a similar incidence of short- and long-term all-cause death between ICR and SCR. Our analysis also reveals a reduction in risk in 1-year MI (46%) and TVR (38%) after ICR at index procedure. Future studies are needed to obtain more precise evidence and identify the cardiovascular benefits of these two strategies.

# Abbreviations

MVD	Multivessel disease
STEMI	ST-segment elevation myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
CR	Complete revascularization
PCI	Percutaneous coronary intervention
ACS	Acute coronary syndrome

ICR	Immediate complete revascularization
SCR	Staged complete revascularization
RCT	Randomized controlled trial
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
TVR	Target vessel revascularization
GRADE	Grading of recommendations assessment, development, and
	evaluation
RR	Risk ratio
TSA	Trial sequential analysis
FFR	Fractional flow reserve

#### **Supplementary Information**

The online version contains supplementary material available at https://doi.or g/10.1186/s12872-024-04414-9.

Supplementary Material 1	
Supplementary Material 2	
Supplementary Material 3	
Supplementary Material 4	
	-

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Not applicable.

#### Author contributions

Xuan-Yan Liu, Jing-Chao Sun and Bin-Hua Ye contributed to the study design, the data acquisition, analysis, interpretation, the drafting, and revision of the manuscript and agreed to be accountable for all aspects of the work. Yan-Yan Li and Xian-Dan Wu contributed to the study conceive, the supervision, data interpretation, and performed revision of the manuscript. Xian Lin and Yue Lin contributed to the study conceive, design, data analysis, interpretation, and revised the manuscript. All authors read and approved the final manuscript.

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#### Data availability

Data is provided within the manuscript.

#### Declarations

**Ethics approval and consent to participate** Not applicable.

#### **Consent for publication** Not applicable.

Competing interests

The authors declare no competing interests.

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