https://doi.org/10.24875/RECICE.M26000572

SUPPLEMENTARY DATA

Supplementary S1

Search strategy:

PubMed/Cochrane

("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields] OR (("multivessel"[All Fields] OR "multivessels"[All Fields]) AND ("coronary disease"[MeSH Terms] OR ("coronary"[All Fields] AND "disease"[All Fields]) OR "coronary disease"[All Fields])) OR ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields])) AND ((((("immediate"[All Fields] OR "immediately"[All Fields]) AND ("multivessel"[All Fields] OR "multivessels"[All Fields]) AND ("percutaneous coronary intervention"[MeSH Terms] OR ("percutaneous"[All Fields] AND "coronary"[All Fields] AND "intervention"[All Fields]) OR "percutaneous coronary intervention"[All Fields])) OR "PCI"[All Fields]) AND ((("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND ("multivessel"[All Fields] OR "multivessels"[All Fields]) AND ("percutaneous coronary intervention"[MeSH Terms] OR ("percutaneous"[All Fields] AND "coronary"[All Fields] AND "intervention"[All Fields]) OR "percutaneous coronary intervention"[All Fields])) OR (("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND ("multivessel"[All Fields] OR "multivessels"[All Fields]) AND "PCI"[All Fields])))) AND ((((("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials"[All Fields] OR "randomised controlled trials"[All Fields]) AND ("clinical"[Title/Abstract] AND "trial"[Title/Abstract])) OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[Publication Type] OR "random*"[Title/Abstract] OR "random allocation"[MeSH Terms] OR "therapeutic use"[MeSH Subheading]) AND ((("controlled clinical trial"[Publication Type] OR

"controlled clinical trials as topic"[MeSH Terms] OR "controlled clinical trials"[All Fields]) AND ("clinical"[Title/Abstract] AND "trial"[Title/Abstract])) OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[Publication Type] OR "random*"[Title/Abstract] OR "random allocation"[MeSH Terms] OR "therapeutic use"[MeSH Subheading]))

Embase:

'heart infarction'/exp AND 'coronary artery disease'/exp AND (immediate AND multivessel AND percutaneous AND coronary AND intervention OR pci OR interventional) AND 'percutaneous coronary intervention'/exp AND (staged AND multivessel AND percutaneous AND coronary AND intervention OR pci OR interventional) AND cardiovascular AND procedure AND ('clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compared':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab) AND ('clinical':ti,ab AND 'trial':ti,ab OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk)

Supplementary S2

Methodology

Sensitive analysis

To assess the robustness of the pooled estimates, we conducted leave-one-out sensitivity analyses. In this approach, the meta-analysis was repeated iteratively after sequentially excluding one trial at a time, thereby evaluating the influence of each individual study on the overall pooled effect size. Results were expressed as RRs with corresponding 95% CI. This analysis allowed us to determine whether any single trial disproportionately influenced the magnitude or direction of the treatment effect. All calculations were performed using the *metafor* package R for MacOs (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria).

Incidence Rate Ratios

Incidence rate ratios (IRRs) were calculated with corresponding 95% confidence intervals (CIs) for the selected outcomes. For each study, incidence rates were derived as the ratio of the number of events to the total person-time at risk. The pooled IRRs were obtained using a random-effects model (DerSimonian and Laird method), given the anticipated heterogeneity among studies. Statistical heterogeneity was assessed using the I^2 statistic, with values >50% indicating substantial heterogeneity. Analyses were performed using R for MacOs (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria) with the *meta* and *metafor* packages. Funnel plots and Egger's test were used to evaluate small-study effects and potential publication bias. A two-sided *P* value <0.05 was considered statistically significant.

Trial sequential analysis

To control the risk of type I and type II errors due to sparse data and repetitive testing in cumulative meta-analyses, we performed a trial sequential analysis (TSA) using TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Copenhagen, Denmark). A sample size–based approach was used to estimate the required information size (RIS), analogous to the sample size calculation in a single randomized controlled trial. The analysis assumed a 30% relative risk reduction (RRR), a two-sided alpha of 5%, a beta of 20% (corresponding to 80% statistical power), and the control event proportion as observed in the meta-analysis. A random-effects model was applied using the DerSimonian and Laird method. Trial sequential monitoring boundaries were constructed to assess whether firm evidence for benefit, harm, or futility had been reached. If the cumulative Z-curve crossed a boundary before the RIS was met, the result was considered conclusive; otherwise, the outcome was classified as inconclusive due to insufficient information.

Meta-regression

To further investigate sources of heterogeneity, we conducted meta-regression analyses restricted to the outcome of reinfarction, as this was the only endpoint that demonstrated a statistically significant difference in the primary meta-analysis. Study-specific log incidence rate ratios (logIRR) and their corresponding standard errors were extracted from each included trial. Variances were calculated as the square of the standard error, and random-effects models were fitted using the restricted maximum likelihood (REML) method. Three prespecified study-level moderators were evaluated in separate univariable models: (1) timing of staged PCI (expressed as the mean or median number of days between the index and staged procedures), (2) diabetes prevalence in the staged PCI group, and (3) hypertension prevalence in the staged PCI group. Given the limited number of available studies, no multivariable models were performed. For each moderator, regression coefficients (β) with 95% CI and corresponding *p* values were reported, representing the change in logIRR per unit increase in the covariate (e.g., per 1 day of staged PCI delay or per 1% increase in comorbidity prevalence). Residual heterogeneity was quantified using τ^2, and the proportion of unexplained variability was summarized with I^2. Statistical significance was defined as a 2-sided $P < .05$. All analyses were performed using the metafor package R for MacOs (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria).

https://doi.org/10.24875/RECICE.M26000572

Table S1. RCTS excluded after full-text review and reasons for exclusion

Study	Design / Population	Reason for exclusion
Nichita-Brendea et al.[1] 2021	RCT; STEMI with multivessel disease	Outcomes were reported predominantly as Kaplan–Meier curves without providing extractable numerical event counts or effect estimates for the prespecified outcomes, precluding reliable quantitative synthesis.
Tarasov et al.[2] 2017	RCT; STEMI with multivessel disease	Several prespecified outcomes (e.g., stroke, acute kidney injury, cardiac death) were not reported separately, and results were largely presented as composite endpoints, preventing consistent outcome-specific pooling.
BIOVASC – Diletti et al.[3] 2023	RCT; mixed ACS population (STEMI, NSTEMI, unstable angina) with multivessel disease	Included a heterogeneous acute coronary syndrome population and did not provide a separate, extractable sub analysis for patients with STEMI and multivessel disease.
SMILE – Sardella et al.[4] 2016	RCT; multivessel NSTEMI	Exclusively enrolled patients with non–ST-segment elevation myocardial infarction; no STEMI population was included.
Elkady et al.[5] 2021	RCT; non–ST-segment elevation acute coronary syndrome	Included only NSTE-ACS patients and explicitly excluded patients with STEMI, not meeting the population eligibility criteria of the present study.

Trials were excluded based on predefined methodological and population-specific criteria to ensure consistency in outcome definitions and quantitative synthesis across studies.

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Table S2. Outcomes definitions

Trial	Outcome	Definition
Sthäli et. al.[6] 2023	Cardiac death	Any death due to a clear cardiac cause (e.g, myocardial infarction (MI), low-output failure, fatal arrhythmia), or unknown cause (unwitnessed death) will be classified as cardiac.
	All-cause mortality	Any death due to a documented non-cardiovascular cause (e.g.trauma, cancer, infection, suicide).
	Reinfarction	Myocardial infarction after the periprocedural period may be secondary to late stent complications or progression of native disease. Performance of electrocardiograms (ECGs) and coronary angiography supports adjudication to either a target or non-target vessel in most cases. All MIs following the index treatment will be recorded. Myocardial infarction will be defined based on the third universal definition.
	Stroke	The definition of stroke includes ischemic and hemorrhagic strokes. An ischemic stroke is defined as an acute focal neurologic deficit that either result in clinical symptoms lasting for at least 24 hours or that was associated with evidence of relevant infarction on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain.
Park et. al.[7] 2023	MACE	Total death, recurrent myocardial infarction (MI), repeat revascularization, and any individual components of MACE.

		Additionally, cardiac death, stent thrombosis, and stroke were adjudicated.
	All deaths	Considered cardiac deaths unless a non-cardiac origin was definitively documented.
	Reinfarction	Recurrent symptoms with new ST-segment elevation or re-elevation of cardiac markers at least twice the upper limit of normal levels.
Wood et. al.[8] 2019	Cardiovascular death	Deaths will be classified as CV or non-CV. All deaths with a clear CV or unknown cause, will be classified as CV. However, within CV deaths, hemorrhagic deaths will be clearly identified. Only deaths due to a documented non-CV cause (e.g., cancer) will be classified as non-CV.
	Myocardial infraction	The definition of MI was based on the Third Universal Definition
Maamoun et. al.[9] 2011	MACE	Including death (cardiac or non-cardiac), recurrent MI, rehospitalization, because of recurrent angina, target vessel revascularization
	Stroke	Any neurologic event whether hemorrhagic or non-hemorrhagic stroke, and bleeding requires surgical intervention and/or blood transfusion.
	Cardiac death	was considered if death was caused by fatal arrhythmia, heart failure, newly occurred MI, or sudden cardiac death.
Politi et. al.[10] 2010	MACE (major adverse cardiac events)	Defined as cardiac or non-cardiac death, in hospital death, re-infarction, re-hospitalization for acute coronary syndrome and repeat coronary revascularization.

Kim et. al. [11] **2025**	Death from any cause	All death will be considered to be cardiac death unless an unequivocal non-cardiac cause can be established
	Unplanned revascularisation	A composite of target-lesion revascularization (TLR), target-vessel revascularization (TVR), and non-TVR.
	Death from cardiac cause	Any death due to proximate cardiac cause
	Non-cardiac death	any death not covered by the aforementioned definitions, such as death caused by infections, including sepsis, malignancy, pulmonary and gastrointestinal diseases, accident, suicide, and trauma.

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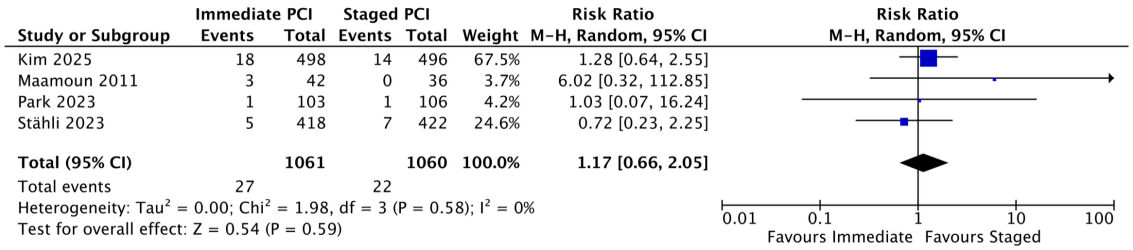

Figure S1. Risk Ratio for Stroke. The Risk Ratio (RR) for stroke across randomized controlled trials are represented by solid squares. The lines denote the 95% confidence intervals (CI) for each study. The bibliographical references mentioned in this figure correspond to: Kim et al.[11] 2025, Stähli et al.[6] 2023, Park et al.[7] 2023, Maamoun et al.[9] 2011.

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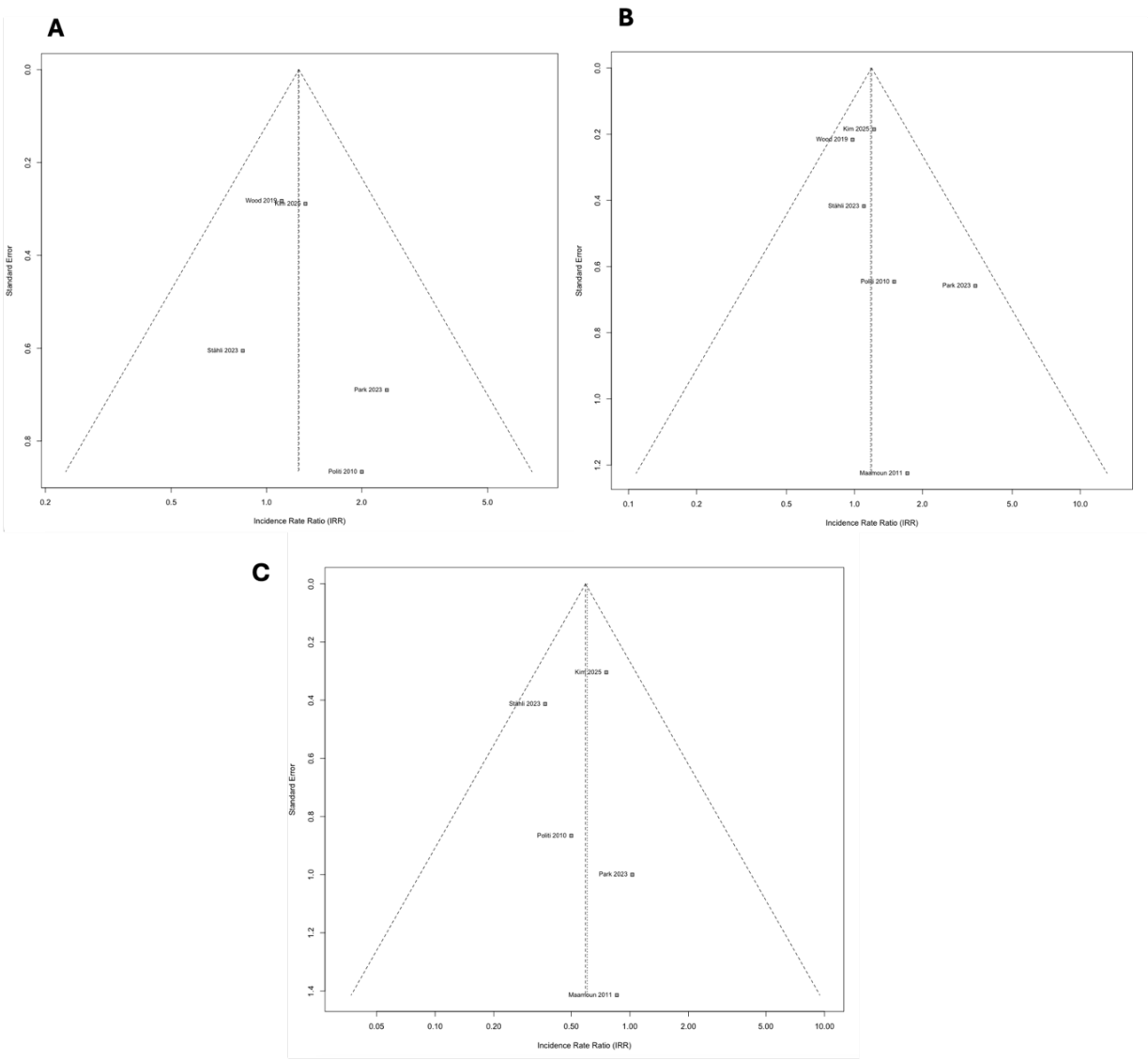

Figure S2. Funnel plot. Publication bias was assessed with funnel plot for A) Cardiac death, B) Death from any cause; and C) Reinfarction.

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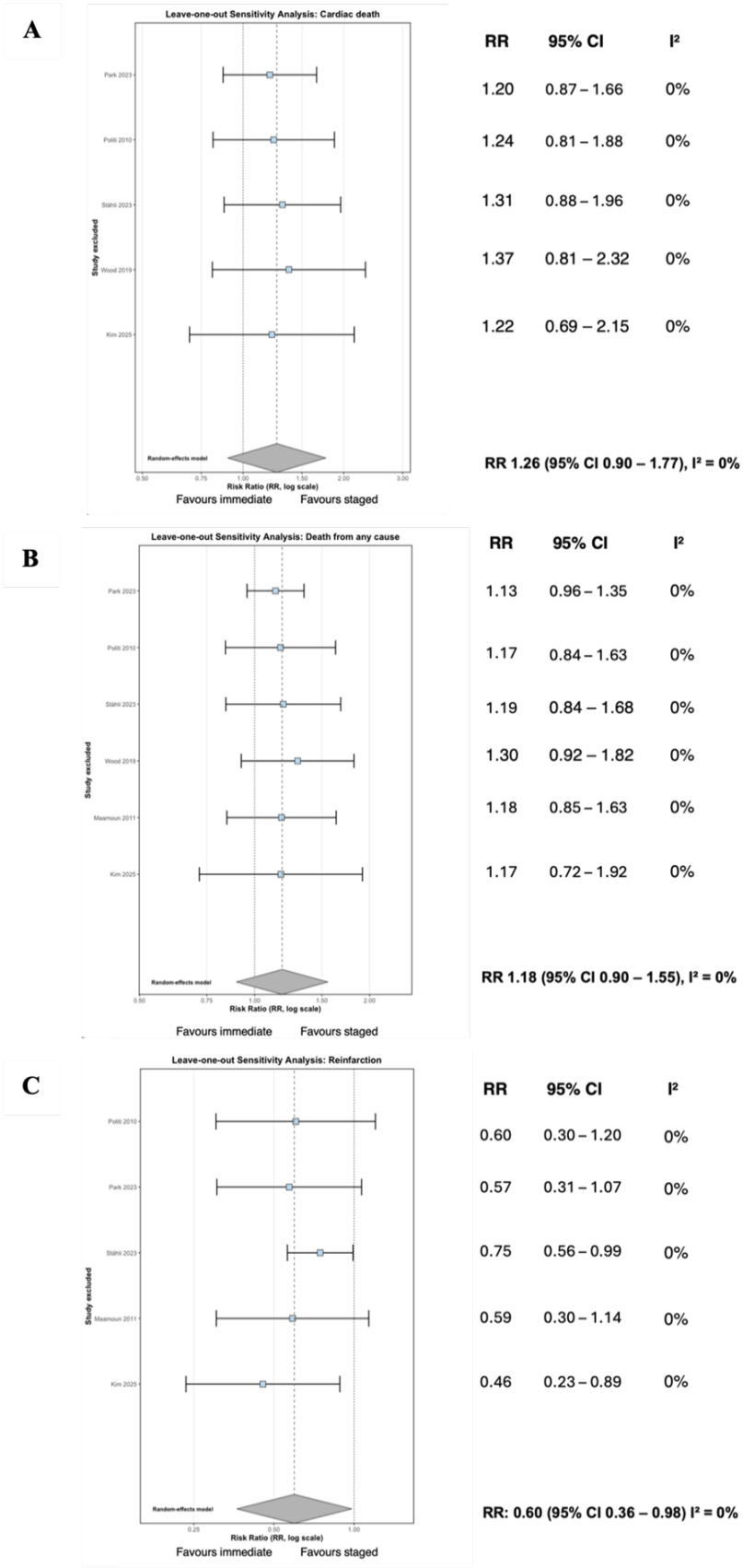

Figure S3. Leave-one-out sensitivity analyses. Leave-one-out sensitivity analyses were conducted for (A) cardiac death, (B) death from any cause, and (C) reinfarction. For each panel, the pooled risk ratio (RR) and 95% confidence interval (CI) were recalculated after sequential exclusion of individual trials.

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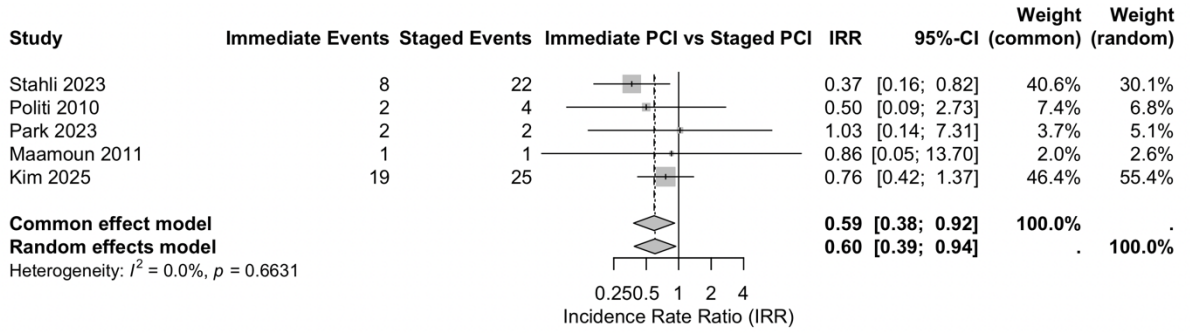

Figure S4. Incidence rate ratio of reinfarction for immediate vs staged PCI. Forest plot of randomized trials comparing reinfarction risk between immediate and staged PCI at 1-year follow-up. Immediate PCI was associated with a significantly lower risk of reinfarction (random-effects IRR: 0.45; 95% CI: 0.23–0.88; p = 0.020). Results were consistent under the common-effect model (IRR: 0.45; 95% CI: 0.23–0.86; p = 0.017). No between-study heterogeneity was observed (I^2 = 0%; Q = 1.15, df = 3; p = 0.77). The bibliographical references mentioned in this figure correspond to: Stähli et al.[6] 2023, Park et al.[7] 2023, Maamoun et al.[9] 2011, Politi et al.[10] 2010, Kim et al.[11] 2025.

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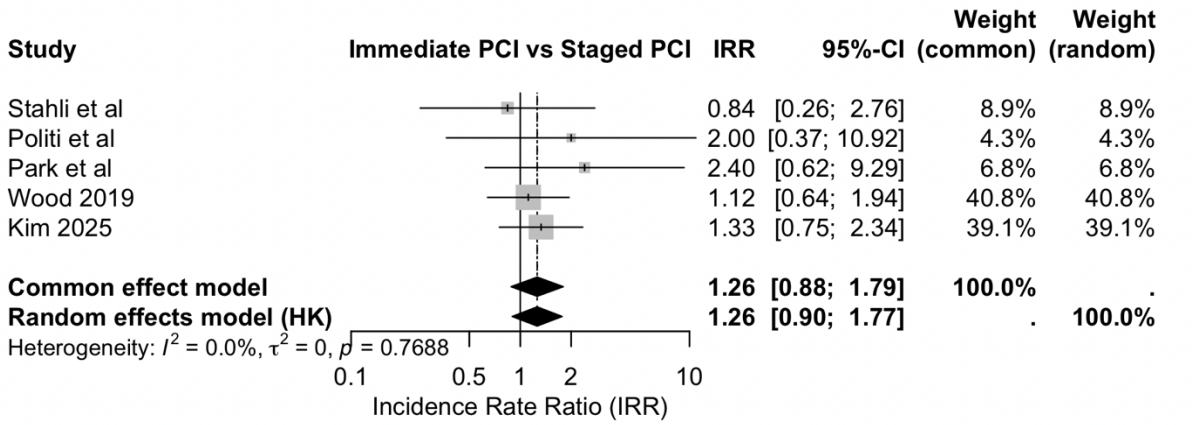

Figure S5. Incidence rate ratio of cardiac death for immediate vs staged PCI. Forest plot of randomized trials comparing reinfarction risk between immediate and staged PCI at 1-year follow-up. Immediate PCI was associated with a significantly lower risk of reinfarction (random-effects IRR: 0.45; 95% CI: 0.23–0.88; p = 0.020). Results were consistent under the common-effect model (IRR: 0.45; 95% CI: 0.23–0.86; p = 0.017). No between-study heterogeneity was observed (I^2 = 0%; Q = 1.15, df = 3; p = 0.77). The bibliographical references mentioned in this figure correspond to: Stähli et al.[6] 2023, Park et al.[7] 2023, Wood et al.[8] 2019, Politi et al.[10] 2010, Kim et al.[11] 2025.

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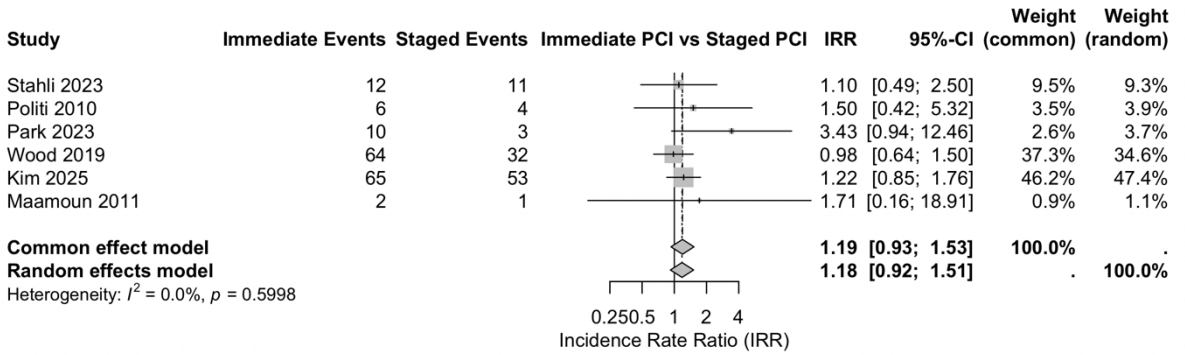

Figure S6. Incidence rate ratio of death from any cause for immediate vs staged PCI. Forest plot of randomized trials comparing all-cause mortality between immediate and staged PCI. Immediate PCI was not associated with a significant difference in risk (random-effects IRR: 1.14; 95% CI: 0.81–1.61; p = 0.45). Findings were consistent with the common-effect model (IRR: 1.16; 95% CI: 0.83–1.64; p = 0.38). No between-study heterogeneity was observed (I^2 = 0%; Q = 3.59, df = 4; p = 0.47). The bibliographical references mentioned in this figure correspond to: Stähli et al.[6] 2023, Park et al.[7] 2023, Wood et al.[8] 2019, Maamoun et al.[9] 2011, Politi et al.[10] 2010, Kim et al.[11] 2025.

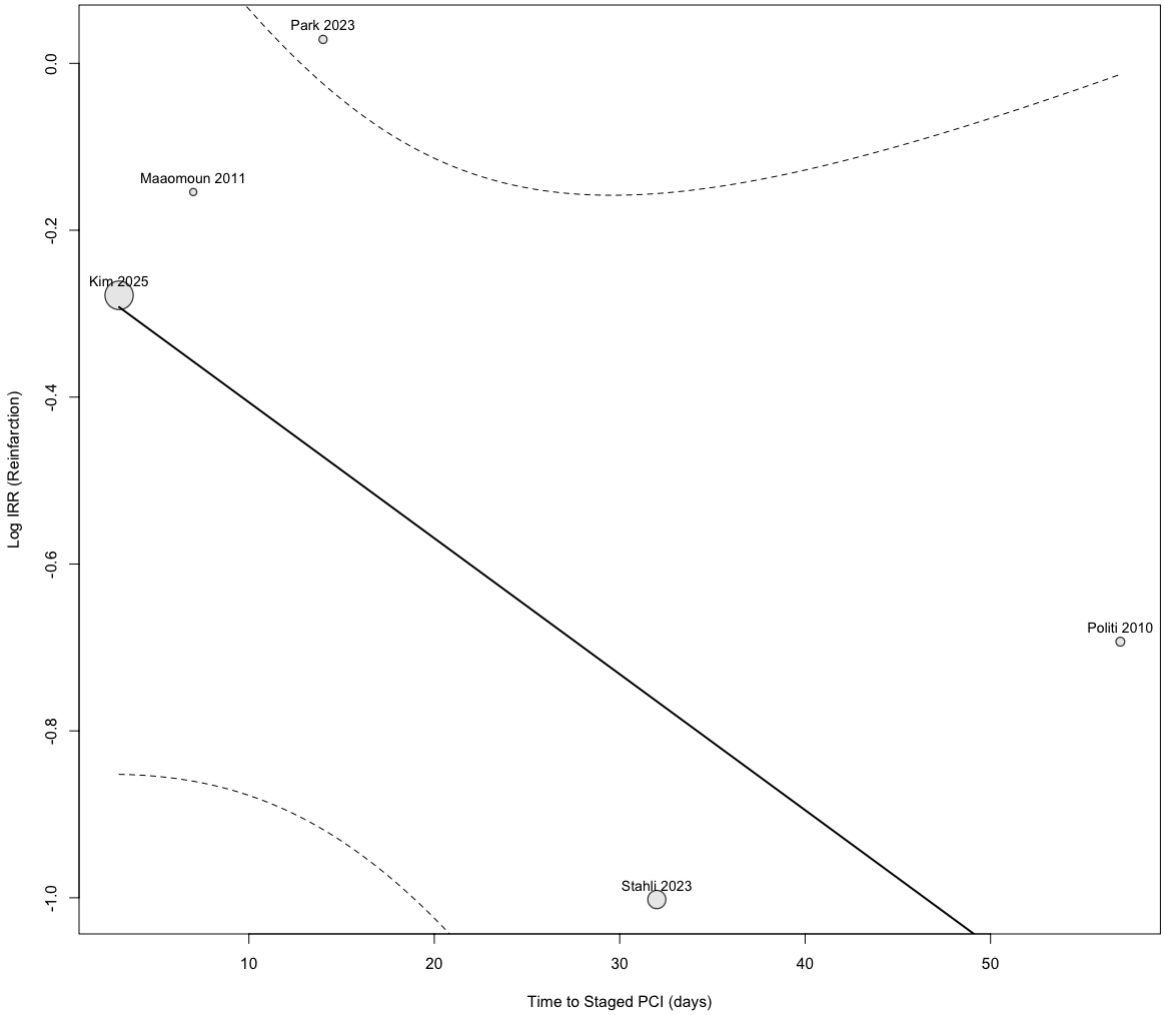

Figure S7. Meta-regression of time to staged PCI and risk of reinfarction. The relationship between time from index procedure to staged PCI (x-axis, days) and log risk ratio of reinfarction (y-axis) is shown. Each circle represents an included trial, with circle size proportional to study weight. The solid line shows the fitted regression slope and the dashed line the 95% confidence interval. The bibliographical references mentioned in this figure correspond to: Stähli et al.[6] 2023, Park et al.[7] 2023, Maamoun et al.[9] 2011, Politi et al.[10] 2010, Kim et al.[11] 2025.

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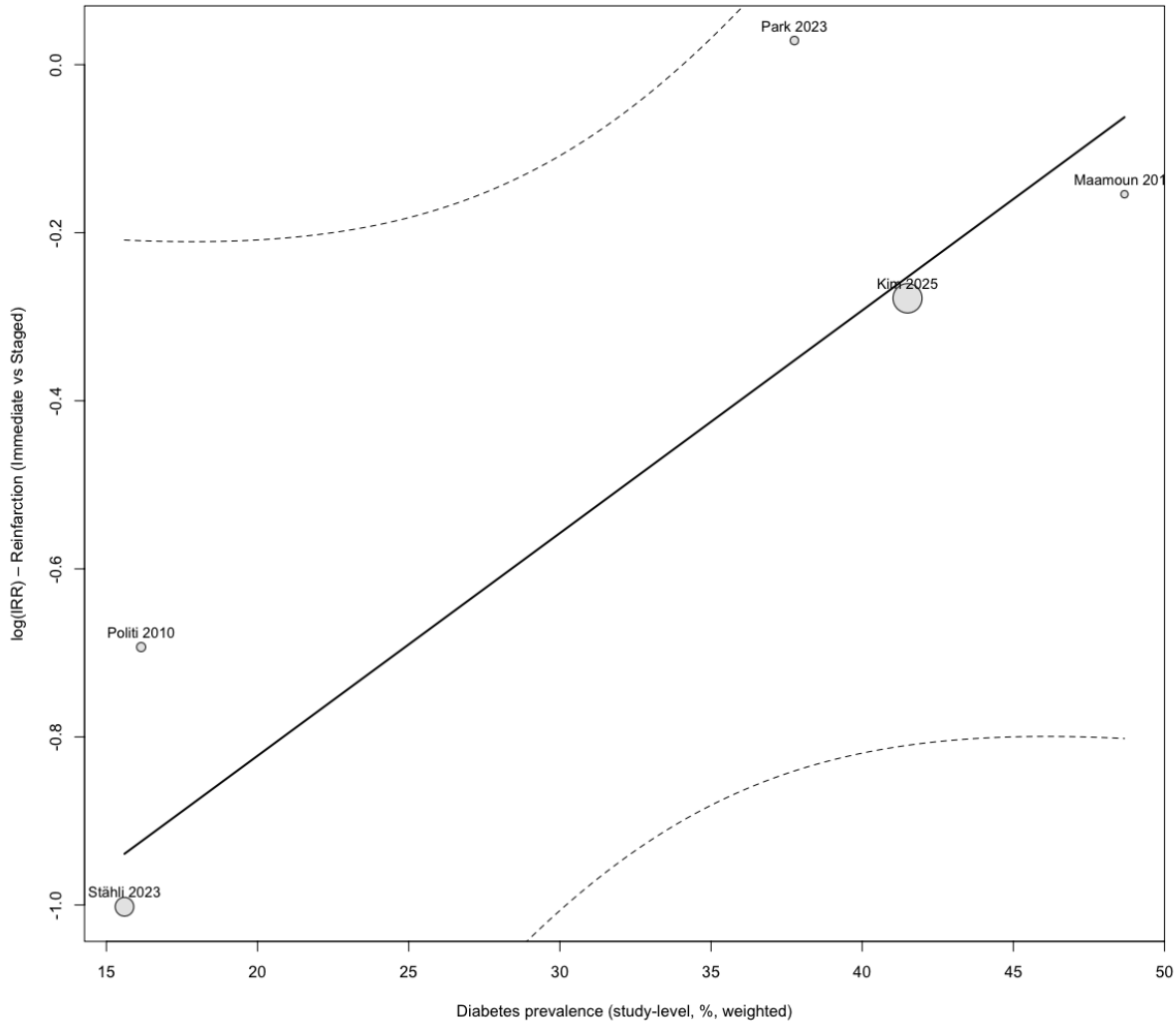

Figure S8. Meta-regression of diabetes prevalence and risk of reinfarction in staged PCI.
Meta-regression assessing the association between diabetes prevalence in the staged PCI group (x-axis, %) and the log incidence rate ratio (IRR) for reinfarction (y-axis). Each circle represents an included trial, with circle size proportional to study weight. The fitted regression slope (solid line) and 95% confidence interval (dashed line) are shown. The bibliographical references mentioned in this figure correspond to: Stähli et al.[6] 2023, Park et al.[7] 2023, Maamoun et al.[9] 2011, Politi et al.[10] 2010, Kim et al.[11] 2025.

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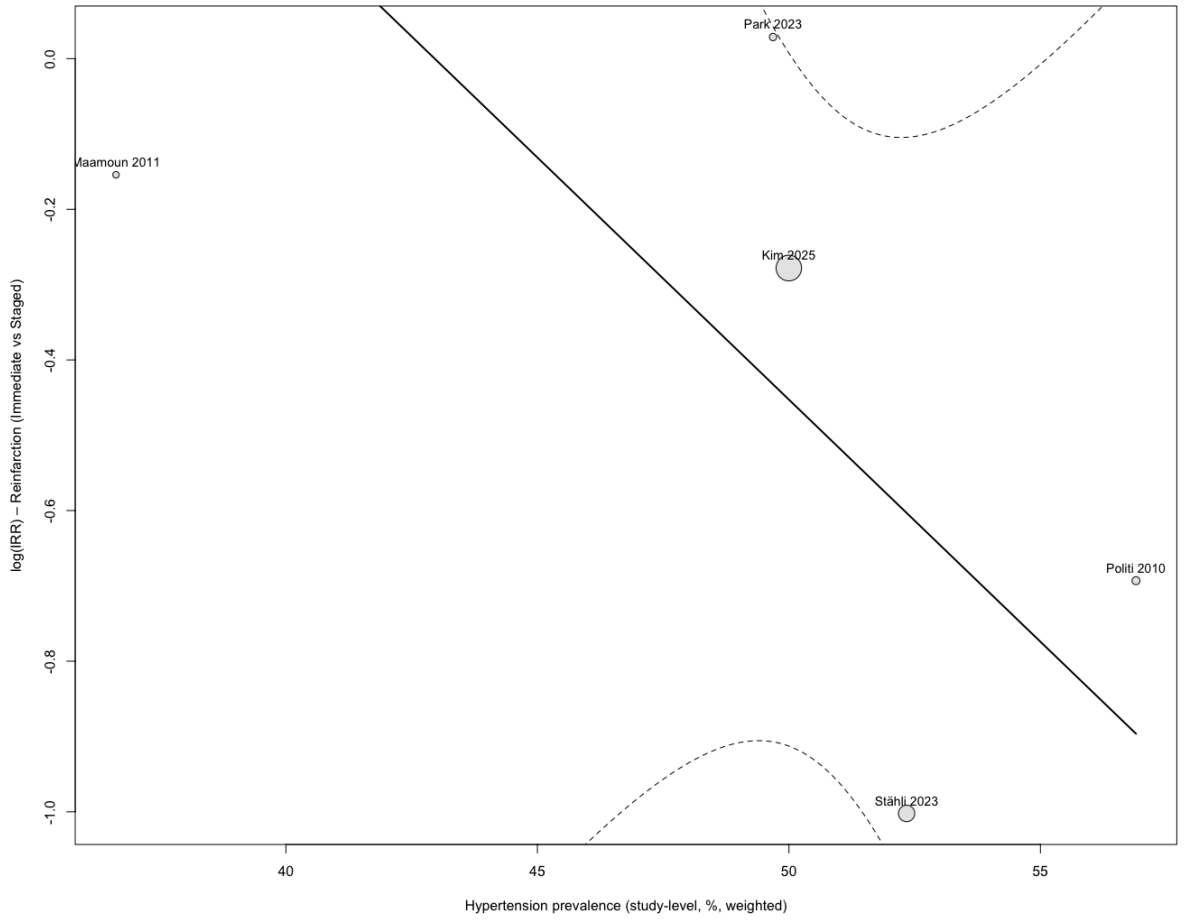

Figure S9. Meta-regression of hypertension prevalence and risk of reinfarction in staged PCI. Meta-regression evaluating the association between hypertension prevalence in the staged PCI group (x-axis, %) and the log incidence rate ratio (IRR) for reinfarction (y-axis). Each circle represents an included trial, with circle size proportional to study weight. The bibliographical references mentioned in this figure correspond to: Stähli et al.[6] 2023, Park et al.[7] 2023, Maamoun et al.[9] 2011, Politi et al.[10] 2010, Kim et al.[11] 2025.

https://doi.org/10.24875/RECICE.M26000572

REFERENCES OF THE SUPPLEMENTARY DATA

1. Nichita-Brendea MT, Popescu MI, Popa V, Carmen PCD. A clinical trial comparing complete revascularization at the time of primary percutaneous coronary intervention versus during the index hospital admission in patients with multi-vessel coronary artery disease and ST-elevation myocardial infarction uncomplicated by cardiogenic shock. *Anatol J Cardiol.* 2021;25:781-788.

2. Tarasov RS, Ganyukov VI, Barbarash OL, Barbarash LS. Two preventive multivessel stenting strategy with zotarolimus eluting stents in STelevation myocardial infarction patients: 12-month results of randomized trial. *Interv Cardiol (Lond).* 2017;9:57-63.

3. Diletti R, den Dekker WK, Bennett J, et al. Immediate versus staged complete revascularisation in patients presenting with acute coronary syndrome and multivessel coronary disease (BIOVASC): a prospective, open-label, non-inferiority, randomised trial. *Lancet.* 2023;401:1172-1182.

4. Sardella G, Lucisano L, Garbo R, et al. Single-Staged Compared With Multi-Staged PCI in Multivessel NSTEMI Patients The SMILE Trial. *J Am Coll Cardiol.* 2016;67:264-272.

5. Elkady AO, Abdelghany M, Diab R, Ezz A, Elagha AA. Total versus staged versus functional revascularization in NSTEACS patients with multivessel disease. *Egypt Heart J.* 2021;73:56.

6. Stähli BE, Varbella F, Linke A, et al. Timing of Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med.* 2023;389:1368-1379.

7. Park S, Rha SW, Choi BG, et al. Immediate versus staged complete revascularization in patients with ST-segment elevation myocardial infarction and multivessel coronary artery disease: results from a prematurely discontinued randomized multicenter trial. *Am Heart J.* 2023;259:58-67.

8. Wood DA, Cairns JA, Wang J, et al. Timing of Staged Nonculprit Artery Revascularization in Patients With ST-Segment Elevation Myocardial Infarction: COMPLETE Trial. *J Am Coll Cardiol.* 2019;74:2713-2723.

9. Maamoun W, Elkhaeat N, Elarasy R. Safety and feasibility of complete simultaneous revascularization during primary PCI in patients with STEMI and multi-vessel disease. *Egypt Heart J.* 2011;63:39-43.

10. Politi L, Sgura F, Rossi R, et al. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. *Heart.* 2010;96:662-667.

11. Kim MC, Ahn JH, Hyun DY, et al. Immediate versus staged complete revascularisation during index admission in patients with ST-segment elevation myocardial infarction and multivessel disease (OPTION–STEMI): a multicentre, non-inferiority, open-label, randomised trial. *Lancet.* 2025;406:1032-1043.