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REVIEW ARTICLE

Early Oral P2Y12 Inhibitor Loading in Patients with ST-segment Elevation Myocardial Infarction Undergoing Primary PCI: A Systematic Review and Meta-analysis

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Abstract: **Introduction:** Whether oral P2Y12 inhibitor loading should be given before hospital arrival or deferred until angiography remains uncertain in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). We compared the efficacy and safety of early loading with later in-hospital, catheterization-laboratory, downstream, or no pretreatment. **Methods:** PubMed/MEDLINE, Embase, Scopus, and Web of Science were searched from inception through July 2026 without a language restriction. Randomized and nonrandomized comparative studies of adults with STEMI undergoing primary PCI were eligible. Primary random-effects meta-analyses used restricted maximum likelihood (REML) when at least three independent studies were available. A direct prehospital analysis was defined in the working analysis plan before final pooling. Because the review was not prospectively registered, these analytical decisions are described as predefined rather than as claims of prospective protocol registration. **Results:** Twenty-six studies were included, comprising three randomized trials and 23 nonrandomized studies. In the primary REML analysis, early P2Y12 loading was associated with higher pre-PCI thrombolysis in myocardial infarction (TIMI) 2/3 flow (8 studies; odds ratio (OR): 1.37, 95% confidence interval (CI): 1.03 to 1.83; p=0.032; I^2=87.5%) and pre-PCI TIMI 3 flow (9 studies; OR: 1.39, 95% CI: 1.03 to 1.88; p=0.029; I^2=83.5%), but neither association retained nominal significance after Knapp–Hartung adjustment. Thirty-day recurrent myocardial infarction/re-infarction was lower in the primary model (10 studies; OR: 0.70, 95% CI: 0.50 to 0.96; p=0.029), although Egger testing suggested possible small-study effects (p=0.079) and leave-one-out analyses were not uniformly stable. Thirty-day stroke was also lower (6 studies; OR: 0.69, 95% CI: 0.56 to 0.85; p<0.001), but this estimate lost significance in sensitivity analysis. Six-month mortality was higher in a three-study primary analysis (OR: 1.18, 95% CI: 1.09 to 1.29; p<0.001), but the Knapp–Hartung CI included the null (0.99 to 1.41) and one registry contributed 99.6% of the random-effects weight. Major bleeding was not increased (14 studies; OR: 1.05, 95% CI: 0.86 to 1.28; p=0.655). **Conclusions:** The certainty of evidence was very low for every pooled outcome-time stratum. Primary analyses suggested possible improvements in pre-PCI patency and selected ischemic outcomes without a detectable increase in major bleeding, but several positive estimates were not robust to Knapp–Hartung or influence analyses. The isolated six-month mortality signal was likewise statistically fragile. Further studies are needed, yet current evidence does not establish a routine pretreatment benefit for oral P2Y12 inhibitor use in all patients with STEMI undergoing primary PCI.

Keywords: ST-Segment Elevation Myocardial Infarction; Percutaneous Coronary Intervention; Ticagrelor; Clopidogrel

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1. Introduction

ST-segment elevation myocardial infarction (STEMI) requires rapid diagnosis and reperfusion. Among patients treated with primary percutaneous coronary intervention (PCI), longer treatment delays are associated with higher mortality, making reduction of total ischemic time a central aim of care (1-3].

Aspirin combined with an oral P2Y12 receptor inhibitor is standard antiplatelet therapy for acute coronary syndrome treated with PCI (1,2]. Ticagrelor and prasugrel provide stronger and more consistent platelet inhibition than clopidogrel and have reduced ischemic events in major acute coronary syndrome trials (4,5). Giving these drugs earlier may increase platelet inhibition before PCI, but it also exposes patients to treatment before coronary anatomy, the final diagnosis, and the possible need for surgery are known (2,6).

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The unresolved issue is therefore one of timing rather than indication. A loading dose given in the ambulance, at a referring hospital, or before angiography has more time to take effect before wire crossing and stent implantation. That interval could improve infarct-related artery patency or reduce periprocedural thrombosis. On the other hand, pretreatment may be unnecessary or harmful when the diagnosis changes, bleeding risk is high, or urgent coronary artery bypass grafting is required (2,6). The balance is particularly difficult in prehospital systems, where treatment is started before coronary anatomy is available.

Randomized trials have not settled this question. In CIPAMI, prehospital clopidogrel 600 mg did not significantly improve pre-PCI thrombolysis in myocardial infarction (TIMI) 2/3 flow, although no clear safety concern emerged (7). Load&Go compared prehospital clopidogrel 600 or 900 mg with peri-interventional clopidogrel 300 mg, but its small sample provided limited information on clinical endpoints (8). ATLANTIC similarly found that prehospital ticagrelor was safe but did not

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improve its primary pre-PCI reperfusion endpoints compared with in-hospital loading (9).

Observational studies have produced less consistent results. Some registries and regional networks reported lower mortality or better reperfusion and ischemic outcomes with earlier treatment (10,36,40). Large contemporary registries, however, found little evidence of benefit for survival, infarct-related artery patency, stent thrombosis, bleeding, or composite outcomes (11-13). These comparisons are vulnerable to differences in transfer pathways, local treatment protocols, the definition of pretreatment, and residual confounding.

The most recent broad meta-analysis found no significant reduction in all-cause mortality, myocardial infarction, or major bleeding with P2Y12 pretreatment, although re-infarction was lower in a prehospital subgroup (14). Several questions remained open. Earlier reviews often combined true prehospital loading with treatment given shortly before angiography or PCI, despite meaningful differences in diagnostic certainty and time available for drug absorption. Reperfusion outcomes were not always examined alongside clinical and bleeding endpoints, and major bleeding was defined differently across studies. Additional registry and cohort data published since those reviews also warranted a new synthesis.

We therefore updated the evidence on early oral P2Y12 inhibitor loading in adults with STEMI undergoing primary PCI. The main analysis included prehospital, upstream, pre-angiography, and pre-PCI loading and compared these strategies with in-hospital, catheterization-laboratory, downstream, delayed, or no pretreatment. A separate analysis was restricted to direct prehospital comparisons. Angiographic, ischemic, and bleeding outcomes were examined by follow-up period, with subgroup analyses for study design, P2Y12 inhibitor group, and bleeding definition when the data were sufficient.

2. Methods

2.1. *Study design*

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (15). The review included adults with STEMI undergoing primary PCI and compared oral P2Y12 loading before angiography or PCI with later in-hospital, catheterization-laboratory, downstream, or no pretreatment. The review was not prospectively registered, and no publicly accessible protocol was available.

2.2. *Eligibility criteria*

Eligible studies enrolled adults with STEMI treated with primary PCI, compared earlier oral P2Y12 loading with delayed or no loading before angiography or PCI, and reported at least one angiographic, ischemic, or bleeding outcome. Clopidogrel, ticagrelor, prasugrel, and mixed oral P2Y12 strategies were eligible. Randomized trials, prospective or retrospective cohorts, registry studies, and electronic health-record studies were considered. For the broad analysis, pretreatment included administration before coronary angiography or PCI, at first medical contact, at a referring hospital, during transfer, or in the ambulance. The predefined direct-prehospital analysis included only studies that directly compared prehospital loading with in-hospital, catheterization-laboratory, or periprocedural loading.

We excluded studies without separately extractable STEMI primary-PCI data, facilitated-PCI studies after fibrinolysis, reports without an eligible timing comparison, and studies in which the main intervention was non-oral or was not a P2Y12 inhibitor. Comparisons of formulation or administration route without a timing contrast were also excluded. Duplicate and substudy reports were retained only when they provided unique outcome data. When populations overlapped, the most appropriate non-overlapping dataset was selected separately for each outcome.

2.3. *Information sources and search strategy*

PubMed/MEDLINE, Embase, Scopus, and Web of Science were searched from database inception to 8 July 2026. No language restriction was applied. The strategy combined terms for STEMI, primary PCI, oral P2Y12 inhibitors, and early or prehospital administration. Search terms covered clopidogrel, ticagrelor, prasugrel, dual antiplatelet therapy, ambulance or emergency medical services, upstream treatment, pretreatment, and pre-angiography loading. Reference lists of eligible articles and relevant reviews were searched manually. Records were imported into a screening database and de-duplicated before title and abstract review; the full strategies are provided in Supplementary Appendix 1.

2.4. *Study selection*

Two reviewers independently screened titles and abstracts and then assessed potentially eligible reports against the prespecified criteria. The most complete report was used when more than one publication described the same study. A conference abstract was eligible when it reported an appropriate comparison and enough numerical information for meta-analysis; lack of a full journal article was not, by itself, a reason for exclusion. Disagreements were resolved by discussion, and reasons for exclusion were recorded for the PRISMA diagram.

2.5. *Data extraction*

Two reviewers independently extracted study and outcome data with a standardized form and resolved discrepancies by returning to the source report. Extracted items included study setting and design, enrollment period, sample size, treatment-group denominators, P2Y12 inhibitor and loading dose, timing and place of administration, comparator strategy, follow-up, outcome definitions, and event counts. We also recorded population restrictions, co-interventions, bleeding definitions, and variables required for subgroup analyses.

Event counts and denominators were preferred. When a report gave group denominators and rounded percentages but not integer event counts, we reconstructed the counts by multiplying the percentage by the denominator and rounding to the nearest whole event. Reconstructed data were used only when the comparison was eligible, unique, and internally consistent. Odds ratios and standard errors were calculated from 2×2 tables; a continuity correction was applied when a zero cell prevented estimation. Articles from overlapping registries could both remain in the review, but they were not allowed to contribute overlapping outcome data to the same pooled estimate.

2.6. *Outcomes*

Outcomes were classified as angiographic or reperfusion endpoints, clinical ischemic endpoints, and bleeding endpoints. Angiographic and reperfusion outcomes were pre-PCI TIMI

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2/3 flow, pre-PCI TIMI 3 flow, post-PCI TIMI 3 flow, no-reflow, ST-segment resolution, myocardial blush grade or TIMI Myocardial Perfusion Grade (TMPG) 3, and infarct-related artery occlusion when reported.

Clinical outcomes included recurrent myocardial infarction or re-infarction, stent thrombosis, all-cause mortality, stroke, and major adverse cardiovascular events. Study-defined major adverse cardiac and cerebrovascular events (MACE/MACCE) and related ischemic composites were analyzed under the common label MACE/MACCE while retaining their original definitions in the extraction file.

Major bleeding was the primary safety outcome. We accepted the definition used by each study, including TIMI score, Bleeding Academic Research Consortium (BARC) Scale, Global Utilization of Streptokinase and Tissue Plasminogen Activator (TPO) for Occluded Arteries (GUSTO) bleeding criteria, and study-defined major bleeding. An outcome was pooled only when at least three independent studies reported it at the same follow-up interval.

2.7. *Risk-of-bias assessment*

Two reviewers assessed risk of bias independently. Randomized trials were evaluated with the revised Cochrane risk-of-bias tool (RoB 2) (16), covering the randomization process, deviations from assigned intervention, missing outcome data, outcome measurement, and selective reporting. Nonrandomized studies were assessed with Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) (17). The domains addressed confounding, participant selection, classification of the intervention, deviations from intended intervention, missing data, outcome measurement, and selection of the reported result. Domain judgments and the overall rating were assigned for each study. Differences between reviewers were resolved by discussion and re-examination of the report.

2.8. *Statistical analysis*

All primary statistical analyses were performed using Stata Statistical Software, Release 18 (StataCorp LLC, College Station, TX, USA) (23). The unit of analysis was an independent study–outcome–follow-up stratum. Angiographic, ischemic, and bleeding outcomes were analyzed separately, and estimates reported at different follow-up intervals were not combined.

Odds ratios (ORs) with 95% confidence intervals (CIs) were used for all dichotomous outcomes. Effect estimates were calculated primarily from the reported numbers of events and participants in the early-loading and comparator groups. Study-specific log ORs and standard errors were pooled using random-effects models with between-study variance estimated by restricted maximum likelihood (REML) (18). Summary estimates were back-transformed and reported as pooled ORs with 95% CIs. Statistical heterogeneity was assessed using Cochran's Q statistic and described using , , and (19). Each outcome was analyzed separately at each reported follow-up interval, including in-hospital or discharge, 30-day, 6-month, and 1-year follow-up. A pooled estimate was produced only when at least three independent studies were available for the same outcome and follow-up interval.

Each study contributed no more than one effect estimate to a given pooled analysis. When a study included more than one eligible early-treatment arm sharing a common comparator, the intervention arms were combined and the comparator group was counted only once. For reports derived from overlapping registries or study populations, only unique outcome data were retained within each outcome-specific meta-analysis to avoid double-counting participants.

The primary analysis used the broad pretreatment definition, which included oral P2Y12 inhibitor administration before coronary angiography or PCI, at first medical contact, at a referring hospital, during transfer, or in the prehospital setting. A separate predefined analysis was restricted to studies directly comparing prehospital loading with in-hospital, catheterization-laboratory, or periprocedural loading. This analysis reflected a narrower treatment-timing contrast and was unrelated to publication type or full-text availability.

Subgroup analyses were predefined in the working analysis plan for study design, P2Y12 inhibitor group, and bleeding definition. Subgroup-specific pooled estimates and categorical between-subgroup meta-regression were reported only when at least two categories each contained three or more independent studies. Follow-up intervals were treated as separate outcome strata rather than as a meta-regression covariate. Categorical meta-regression coefficients were interpreted on the log-OR scale. Continuous meta-regression by sample size was not part of the final analysis.

Because conventional random-effects confidence intervals can be unstable with few studies, sensitivity analyses were done using the Knapp–Hartung standard-error adjustment for every outcome–follow-up stratum with fewer than 10 studies, while retaining REML for τ^2 estimation. Leave-one-out analyses were performed for every broad-analysis stratum when deleting one study left at least three studies available for pooling. For highly heterogeneous outcomes, a post hoc exploratory analysis contrasted direct prehospital studies with other early/upstream definitions.

Potential small-study effects were assessed only for outcomes reported by at least 10 independent studies. Funnel plots were generated using Stata's official meta funnel plot command, and Egger's regression and Begg's rank-correlation tests were performed with meta bias (20,21,23). A two-sided p value below 0.10 was considered suggestive of possible small-study effects. For primary pooled treatment effects and between-subgroup meta-regression, two-sided p values below 0.05 were considered statistically significant.

2.9. *Certainty of evidence*

Certainty of evidence was graded for all pooled outcome–time strata using Grading of Recommendations Assessment, Development and Evaluation (GRADE) checklist (22). Ratings considered risk of bias, inconsistency, indirectness, imprecision, and publication bias. Because most evidence was nonrandomized, certainty generally started at low and was downgraded when additional concerns were present.

3. Results

3.1. *Study selection*

The searches identified 1,499 records: 181 from PubMed, 637 from Embase, 388 from Scopus, and 293 from Web of Science. After 568 duplicates were removed, 931 records underwent title and abstract screening; 893 were excluded. Thirty-eight reports were sought and all 38 were retrieved and assessed for eligibility. Twelve reports were excluded because they represented duplicate or overlapping datasets without unique

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eligible outcome data (n=4), were not true pretreatment comparisons (n=2), did not provide outcome data suitable for the meta-analysis (n=5), or used the wrong intervention or comparison (n=1). Twenty-six studies contributed quantitative data (7-13,24-40,42,51). Figure 1 shows the reconciled PRISMA flow.

3.2. *Study characteristics*

The 26 quantitative studies included are described in Table 1. Three were randomized trials and 23 were nonrandomized studies based on registries, cohorts, electronic health records, or a conference abstract. Publications ranged from 2008 to 2026. Clopidogrel dominated the earlier literature; ticagrelor was studied in ATLANTIC and several later cohorts, whereas recent registries often combined P2Y12 inhibitors. Pretreatment ranged from ambulance or first-medical-contact loading to treatment shortly before angiography or PCI. Three included reports used Swedish Coronary Angiography and Angioplasty registry (SCAAR)-based data. Koul (2011) enrolled patients from 2003–2008 (30), Koul (2018) from October 2010–October 2014 (12), and Redfors (2019) from 2005–2016 (11). Koul (2011) therefore overlapped Redfors by calendar years during 2005–2008, but the final meta-analysis used Koul (2011) only for 1-year outcomes and Redfors (2019) only for 30-day outcomes, so the two reports never contributed to the same outcome–follow-up pool. Koul (2018), which also overlapped Redfors, contributed only its unique 30-day composite endpoint; its overlapping mortality, myocardial infarction (MI), stent-thrombosis, and bleeding components were excluded. Kovacevic (2025) was included because the abstract reported an eligible comparison, group denominators, and percentages sufficient to reconstruct event counts; its influence was examined by exclusion sensitivity analysis.

3.3. *Angiographic and reperfusion outcomes*

In the primary broad REML analysis, early or upstream P2Y12 loading was associated with higher pre-PCI TIMI 2/3 flow (8 studies; OR: 1.37, 95% CI: 1.03 to 1.83; p=0.032; I^2=87.5%) and pre-PCI TIMI 3 flow (9 studies; OR: 1.39, 95% CI: 1.03 to 1.88; p=0.029; I^2=83.5%). The very high I^2 values indicate that these pooled ORs represent heterogeneous average associations rather than a common study effect. With Knapp–Hartung adjustment, the corresponding CIs widened to 0.96–1.95 (p=0.076) and 0.96–2.01 (p=0.071), respectively. A post hoc timing analysis yielded OR: 1.71 (95% CI: 1.21 to 2.41) for direct prehospital versus in-hospital comparisons and OR: 1.09 (95% CI: 0.77 to 1.55) for other early/upstream definitions for TIMI 2/3 flow (interaction p=0.071); for TIMI 3 flow, the corresponding ORs were 1.76 (95% CI: 1.08 to 2.89) and 1.12 (95% CI: 0.82 to 1.53) (interaction p=0.155). Thus, timing definition did not clearly account for the heterogeneity. Post-PCI TIMI 3 flow (10 studies; OR: 1.09, 95% CI: 0.82 to 1.44; p=0.569; I^2=73.9%) and no-reflow (7 studies; OR: 0.75, 95% CI: 0.53 to 1.06; p=0.105; I^2=38.9%) did not differ significantly. Figures 2 and 3 and Supplementary Tables S2–S5 provide the primary and sensitivity results.

3.4. *Clinical ischemic outcomes*

At 30 days, the primary analysis showed fewer recurrent MI/re-infarction events (10 studies; OR: 0.70, 95% CI: 0.50 to 0.96; p=0.029; I^2=40.0%) and strokes (6 studies; OR: 0.69, 95% CI: 0.56 to 0.85; p<0.001; I^2=0.0%). The recurrent-MI result showed possible small-study effects by Egger testing (p=0.079) and lost nominal significance when either Larson (2010) or Postma (2014) was omitted. The stroke result retained significance with Knapp–Hartung adjustment (OR: 0.69, 95% CI: 0.58 to 0.82; p=0.003) but became null after Qadeer (2026) was excluded (OR: 0.84, 95% CI: 0.47 to 1.50; p=0.558); Qadeer contributed 86.3% of the random-effects weight for this outcome. Thirty-day stent thrombosis, all-cause mortality, and MACE/MACCE remained non-significant in the primary models. In-hospital recurrent MI, stent thrombosis, mortality, MACE/MACCE, and stroke were also not significantly different. Cardiogenic shock was lower in the three-study primary model (OR: 0.67, 95% CI: 0.53 to 0.85; p<0.001), but the Knapp–Hartung CI included the null (0.42 to 1.07; p=0.067); this association is also especially vulnerable to reverse causation and confounding by indication because patients presenting in or rapidly progressing to shock may be less likely to receive oral pretreatment. At 6 months, recurrent MI/re-infarction was lower in the primary model (3 studies; OR: 0.77, 95% CI: 0.65 to 0.91; p=0.002), but not after Knapp–Hartung adjustment (95% CI: 0.52 to 1.14; p=0.102). Six-month all-cause mortality was higher in the primary model (3 studies; OR: 1.18, 95% CI: 1.09 to 1.29; p<0.001); however, its Knapp–Hartung CI included the null (95% CI: 0.99 to 1.41; p=0.054), and Qadeer (2026) contributed 99.6% of the random-effects weight, leaving only two studies if omitted. One-year recurrent MI/re-infarction remained lower with Knapp–Hartung adjustment (OR: 0.79, 95% CI: 0.64 to 0.97; p=0.034) and across leave-one-out analyses, whereas 1-year mortality and MACE/MACCE were not significantly different. Figures 4–9 show the primary outcome-specific analyses; Supplementary Tables S2–S4 show sensitivity and influence analyses.

3.5. *Safety outcome*

Pretreatment was not associated with more major bleeding. For in-hospital or discharge major bleeding, the pooled OR was 1.05 (14 studies; 95% CI: 0.86 to 1.28; p=0.655; I^2=24.3%). The 30-day estimate was also null (4 studies; OR: 0.97, 95% CI: 0.85 to 1.12; p=0.688; I^2=0.0%). Any bleeding before discharge was numerically more frequent but not statistically significant (5 studies; OR: 1.34, 95% CI: 0.85 to 2.11; p=0.202; I^2=66.6%). These analyses are shown in Figure 10.

3.6. *Prehospital vs. in-hospital administration of P2Y12 inhibitors*

When the analysis was restricted to direct prehospital comparisons, primary REML estimates favored prehospital loading for pre-PCI TIMI 2/3 flow (4 studies; OR: 1.71, 95% CI: 1.21 to 2.41; p=0.002; I^2=72.0%), pre-PCI TIMI 3 flow (5 studies; OR: 1.76, 95% CI: 1.08 to 2.89; p=0.025; I^2=79.5%), and 30-day recurrent MI/re-infarction (3 studies; OR: 0.52, 95% CI: 0.31 to 0.87; p=0.012; I^2=0.0%). None of these three associations retained nominal significance after Knapp–Hartung adjustment: the corresponding 95% CIs were 0.96–3.06 (p=0.061), 0.88–3.54 (p=0.086), and 0.24–1.13 (p=0.068). Post-PCI TIMI 3 flow, 30-day mortality, in-hospital mortality, and major bleeding remained non-significant. Supplementary Figures S1–S3 show the primary strict analyses and Supplementary Table S2 shows the Knapp–Hartung sensitivity results.

3.7. *Sensitivity and influence analyses*

Knapp–Hartung sensitivity analyses were performed for every stratum with fewer than 10 studies. In the broad analysis, nominal significance was not retained for pre-PCI TIMI 2/3 flow, pre-PCI TIMI 3 flow, in-hospital cardiogenic shock, 6-month mortality, or 6-month recurrent MI. The 30-day stroke

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and 1-year recurrent-MI estimates remained nominally significant. In the direct prehospital analysis, all three primary positive estimates-pre-PCI TIMI 2/3 flow, pre-PCI TIMI 3 flow, and 30-day recurrent MI-crossed the null after Knapp–Hartung adjustment. Full results are reported in Supplementary Table S2.

Leave-one-out analyses also showed instability in several primary findings. Significance for pre-PCI TIMI 2/3 flow was lost after omitting Fabris (2022), Pepe (2018), Postma (2014), or Tohamy (2026); significance for pre-PCI TIMI 3 flow was lost after omitting Fabris (2022), Lupi (2016), Tohamy (2026), or Kovacevic (2025). The 30-day recurrent-MI result became nonsignificant after omission of Larson (2010) or Postma (2014), and the 30-day stroke result became nonsignificant after omission of Qadeer (2026). By contrast, the 1-year recurrent-MI association remained significant after every single-study deletion. For the k=3 analyses, leave-one-out pooling was not performed because deletion left only two studies. Excluding Kovacevic changed pre-PCI TIMI 3 flow from OR 1.39 (95% CI: 1.03 to 1.88; p=0.029) to 1.38 (95% CI: 0.98 to 1.94; p=0.069), while in-hospital and 30-day mortality remained non-significant. Excluding Redfors did not materially change 30-day mortality or stent thrombosis. Targeted influence results for Qadeer, Redfors, and Kovacevic are provided in Supplementary Tables S3 and S4.

3.8. *Subgroup and meta-regression analyses*

Table 2 reports the predefined subgroup analyses that met the minimum data requirement of two categories with at least three independent studies each. P2Y12 inhibitor group was associated with different treatment estimates for 30-day recurrent MI/re-infarction (global meta-regression p<0.001), 30-day stent thrombosis (p=0.019), and in-hospital recurrent MI/re-infarction (p=0.003). In each case, clopidogrel studies produced more favorable estimates than studies of mixed P2Y12 strategies. No interaction was detected for pre-PCI TIMI 3 flow by drug group (p=0.289); post-PCI TIMI 3 flow by design (p=0.883) or drug group (p=0.357); in-hospital mortality (p=0.718) or 30-day mortality (p=0.175) by drug group; or in-hospital/discharge major bleeding by drug group (p=0.059) or bleeding definition (p=0.150).

3.9. *Small-study effects and publication bias*

Six broad-analysis outcomes were reported by at least 10 studies and were assessed for small-study effects. Egger and Begg tests were negative for post-PCI TIMI 3 flow (p=0.612 and p=1.000), 30-day mortality (p=0.956 and p=0.846), in-hospital mortality (p=0.774 and p=0.252), and in-hospital/discharge major bleeding (p=0.350 and p=0.381). For 30-day recurrent MI/re-infarction, the Egger result was suggestive (p=0.079) but the Begg result was not (p=0.858); this caveat is relevant because recurrent MI was one of the nominally favorable primary results. For 30-day stent thrombosis, the Begg test was positive (p=0.049) while the Egger test was not (p=0.110). None of the direct prehospital outcomes reached the 10-study threshold. Funnel plots and test results are provided in Supplementary Appendix 3.

3.10. *Risk of bias assessment*

RoB 2 was applied to the three randomized trials: one was rated at low risk of bias and two had some concerns. Of the 23 nonrandomized studies assessed with ROBINS-I, six were rated at moderate risk and 17 at serious risk. Recurring concerns were confounding by indication, nonrandom allocation of loading time, misclassification of exposure in registry or electronic health-record data, overlap between registry populations, and incomplete reporting in conference abstracts. Tables 3 and 4 give the domain-level judgments.

3.11. *Certainty of evidence*

GRADE was applied to all 32 pooled outcomes–time strata: 25 in the broad pretreatment analysis and seven in the direct prehospital comparison (Table 5). Certainty was very low for every stratum. Most estimates were based mainly on nonrandomized studies with serious risk of bias. Additional concerns included substantial inconsistency, variation in pretreatment and outcome definitions, sparse outcome-specific evidence, imprecision, possible small-study effects for 30-day recurrent MI and stent thrombosis, and lack of robustness of several positive estimates in Knapp–Hartung or influence analyses. The statistically significant primary estimates are therefore treated as uncertain, hypothesis-generating associations rather than definitive treatment effects.

4. Discussion

From a clinical perspective, the current evidence does not support routine early oral P2Y12 loading before PCI in all patients with STEMI. The timing of loading should remain individualized, particularly according to hemodynamic stability, anticipated time to the catheterization laboratory, bleeding risk, and the likelihood of impaired oral drug absorption. Across 26 studies, the primary REML analyses suggested several potential benefits of earlier loading, including improved pre-PCI TIMI flow and lower rates of 30-day recurrent MI and stroke. However, most of these associations were not robust to Knapp–Hartung adjustment or leave-one-out analyses. The reduction in 1-year recurrent MI was the most statistically stable favorable finding, while major bleeding was not increased. Nevertheless, because the certainty of evidence was rated very low across all pooled outcomes, these findings should be regarded as uncertain, hypothesis-generating associations rather than evidence of a definitive treatment benefit.

The clinical question is narrower than whether patients with STEMI should receive a P2Y12 inhibitor. Current guidelines support dual antiplatelet therapy for acute coronary syndrome treated with PCI and generally favor ticagrelor or prasugrel over clopidogrel in suitable patients (1,2). What remains uncertain is whether the loading dose should be given before hospital arrival or coronary angiography. Earlier administration offers more time for absorption and platelet inhibition, but it also commits treatment before the coronary anatomy and, occasionally, the diagnosis are confirmed.

The two headline angiographic estimates require particular caution because heterogeneity was very high (I^2=87.5% for pre-PCI TIMI 2/3 flow and 83.5% for TIMI 3 flow). An exploratory split by timing definition showed larger ORs in direct prehospital comparisons than in other early/upstream comparisons, but interaction tests were not significant (p=0.071 and p=0.155), so this distinction did not clearly explain the between-study variability. Leave-one-out analyses further showed that the nominal significance of both pooled pre-PCI estimates depended on several individual studies. We therefore retained the random-effects summaries as average associations across clinically related studies, but they should not be read as a single effect expected in all treatment pathways.

The contrast between pre-PCI and post-PCI findings is consistent with a possible early patency effect, but it does not

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establish one. Earlier loading was associated with more favorable pre-PCI flow in the primary models, whereas post-PCI TIMI 3 flow and no-reflow were not clearly different. Given the heterogeneity and sensitivity of the pre-PCI estimates, the data do not support a firm mechanistic conclusion about epicardial or microvascular reperfusion.

The randomized trials are less persuasive than the primary pooled observational signal. ATLANTIC found that prehospital ticagrelor was safe but did not improve its coprimary pre-PCI reperfusion endpoints (9), although later analyses reported possible benefits for selected early outcomes and subgroups (44,45). CIPAMI likewise found no significant improvement in pre-PCI TIMI 2/3 flow with prehospital clopidogrel (7). In the direct-prehospital meta-analysis, the primary REML estimates for both pre-PCI TIMI endpoints were significant, but only four and five studies contributed and heterogeneity was substantial; both CIs crossed the null after Knapp–Hartung adjustment. The direct-prehospital 30-day recurrent-MI result behaved similarly. These findings should not be taken as a substitute for adequately powered randomized evidence.

The six-month mortality estimate points in the unfavorable direction and deserves the same attention as the favorable primary results. Mortality was not significantly different in hospital or at 30 days, was higher at 6 months in the three-study primary model (OR 1.18, 95% CI 1.09 to 1.29), and was again nonsignificant at 1 year. This isolated temporal pattern is difficult to reconcile with a persistent causal effect of loading time. It was also statistically fragile: the Knapp–Hartung CI included 1.0 (0.99 to 1.41), and Qadeer (2026) supplied 99.6% of the random-effects weight; without that study, only two studies remained. Sparse data, residual confounding, and chance are therefore more plausible explanations than a proven delayed mortality hazard, although the signal cannot simply be ignored.

The apparent reduction in in-hospital cardiogenic shock is similarly uncertain. Only three nonrandomized studies contributed, the Knapp–Hartung estimate was no longer significant (OR 0.67, 95% CI 0.42 to 1.07), and confounding by indication is especially likely. Patients who present in shock or deteriorate rapidly may be unable to take or absorb an oral loading dose and may proceed directly to the catheterization laboratory; such patients are therefore less likely to be classified as pretreated. Reverse causation can consequently create an apparent protective association even when pretreatment does not prevent shock.

Bellemain-Appaix et al. reported more favorable effects in a meta-analysis of seven randomized trials involving 9,648 patients with STEMI: early P2Y12 inhibition reduced MACE and MI, decreased bail-out glycoprotein IIb/IIIa inhibitor use, and improved pre-PCI TIMI 2/3 flow without increasing major bleeding (46). The present review used a different analytic approach. Angiographic and clinical outcomes were kept separate, broad pretreatment was distinguished from direct prehospital loading, and each follow-up interval required at least three independent studies. We also included later registry and cohort studies. These choices produced a more outcome-specific and generally more conservative interpretation.

Our primary estimates are closer to the meta-analysis by Gewehr et al., which included three randomized trials and 14 observational studies and found no overall reduction in mortality, MI, or major bleeding (14). In the present dataset, 30-day recurrent MI/reinfarction was lower in the primary model, but the result showed possible small-study effects by Egger testing and was not stable to all leave-one-out exclusions; 30-day mortality and major bleeding were null. Differences between reviews may reflect additional contemporary studies, follow-up-specific pooling, and outcome-level handling of overlapping registry populations.

Chou et al. focused specifically on prehospital versus in-hospital administration and reported better TIMI-flow outcomes, fewer recurrent MIs, and no increase in major bleeding (47). The primary direct-prehospital estimates in our analysis pointed in the same direction, but the three nominally favorable outcomes did not retain $p<0.05$ after Knapp–Hartung adjustment. Post-PCI TIMI 3 flow, mortality, and bleeding remained nonsignificant. The direct-prehospital evidence is therefore compatible with a possible benefit, but too sparse for a firm conclusion.

Recent registries illustrate why nonrandomized evidence is difficult to interpret. In the Bern-PCI Registry, Rohla et al. found no association between pretreatment and MACCE despite a clear difference in loading-to-angiography time (13). Almendro-Delia et al., by contrast, reported a time-dependent reduction in 30-day MACE without more bleeding among transferred patients (25). Earlier treatment in routine practice is not assigned at random. It may track transfer status, diagnostic certainty, symptom duration, hemodynamic condition, bleeding risk, vascular access, morphine use, and local emergency medical service protocols. Adjustment can reduce, but not remove, these differences.

Pharmacology also limits the assumption that an earlier tablet necessarily produces effective inhibition by the time of PCI. Gastrointestinal absorption may be slowed in STEMI by nausea, vomiting, impaired perfusion, shock, and opioid treatment. Morphine delays the exposure and antiplatelet effect of oral P2Y12 inhibitors in myocardial infarction (48,49). When transport and door-to-balloon times are short, even prehospital administration may leave too little time for full drug effect before wire crossing.

The absence of a major-bleeding signal was consistent across the broad and direct prehospital analyses and agrees with earlier STEMI meta-analyses (14,46,47). It should not be interpreted as proof that pretreatment is equally safe for every patient. Bleeding definitions varied from TIMI and BARC to GUSTO and study-specific criteria. Registry studies may miss bleeding events or selectively exclude patients at greatest risk. Evidence from non-ST-elevation acute coronary syndromes is not directly applicable to STEMI, but the lack of ischemic benefit and concern about bleeding with routine pretreatment in that setting illustrate why diagnostic certainty and expected time to angiography matter (50).

The drug-group interactions require restraint. Clopidogrel studies showed more favorable estimates than mixed-P2Y12 studies for in-hospital recurrent MI, 30-day recurrent MI, and 30-day stent thrombosis. These are between-study comparisons, not randomized drug-by-timing comparisons. Drug category is entangled with publication year, study design, transfer pathway, adjunctive treatment, stent technology, and outcome definition. The results are useful for generating questions, but they do not justify choosing a loading strategy on the basis of these subgroup estimates.

Multiplicity also affects interpretation. The review contains 32 pooled outcome–time strata in addition to subgroup/meta-regression analyses and the direct-prehospital analyses, and no

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multiplicity adjustment was applied. Some nominally significant findings can therefore arise by chance even in the absence of a reproducible treatment effect. This concern is reinforced by the small-study signal for 30-day recurrent MI and by the influence analyses described above. The individual p values are best viewed as descriptive and hypothesis-generating rather than as multiple independent confirmatory tests.

4.1. *Limitations*

Several limitations affect the certainty of the pooled estimates. Most studies were nonrandomized, and pretreatment ranged from ambulance loading 60–120 minutes before PCI to administration shortly before angiography. One AMI–cardiogenic-shock cohort was not confined to primary PCI; a before–after study changed other first-medical-contact antithrombotic treatment together with early ticagrelor; and event counts for Kovacevic (2025) were reconstructed from rounded percentages. Excluding Kovacevic rendered the pre-PCI TIMI 3 estimate non-significant, although mortality estimates remained null. Three SCAAR-based reports overlapped in calendar periods, requiring outcome- and follow-up-specific adjudication to prevent double-counting. Finally, the large number of outcome–time and exploratory analyses, together with statistical fragility in several small-k strata, increases the possibility of chance findings. These limitations are consistent with the very-low GRADE certainty across all pooled strata.

5. Conclusions

Current evidence does not establish a routine clinical benefit of early oral P2Y12 loading before primary PCI in all patients with STEMI. Although the primary analyses suggested possible improvements in pre-PCI coronary patency and selected ischemic outcomes without an apparent increase in major bleeding, several favorable estimates were not robust to Knapp–Hartung adjustment or influence analyses, and no consistent reduction in mortality, MACE/MACCE, or stent thrombosis was demonstrated. Given the very low certainty of evidence across all pooled outcomes, these findings should be considered hypothesis-generating rather than definitive treatment effects. In clinical practice, the timing of P2Y12 loading should therefore remain individualized according to hemodynamic status, bleeding risk, expected time to PCI, and the likelihood of impaired oral absorption. Adequately powered contemporary randomized trials with clearly defined treatment timing are needed to determine whether specific patient groups benefit from earlier loading.

6. Declarations

6.1. *Acknowledgments*

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6.2. *Conflict of interests*

None.

6.3. *Funding and supports*

None.

6.4. *Authors' contributions*

Pshtiwan Hussein Qadir was responsible for the study conception, literature screening and eligibility decisions, data extraction and verification, risk-of-bias assessment, statistical analysis and interpretation, drafting and revision of the manuscript, final approval, and accountability for the work.

6.5. *Ethical statement*

Not applicable.

6.6. *Informed consent*

Not applicable.

6.7. *Availability of supporting data*

All the data are presented in the paper.

6.8. *Using artificial intelligence chatbots statement*

Artificial intelligence-assisted tools were used only for English-language editing. The author reviewed and verified all content and takes full responsibility for the integrity and accuracy of the manuscript.

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Table 1. Characteristics of quantitative studies included in the meta-analysis

Study	Country	Design	Sample size	PreT / comparator n	P2Y12i / dose	Pretreatment timing/place	Comparator timing/place	Follow-up	Outcomes contributed
Alexander (2008)	United States	Registry-based cohort	3,785	1,029 / 2,756	clopidogrel with or without glycoprotein IIb/IIIa inhibitor context; NR	clopidogrel administered more than 15 minutes before PCI according to the upstream-treatment definition	peri-PCI clopidogrel administered less than 15 minutes before, during, or after PCI	in-hospital	in-hospital death, recurrent MI, cardiogenic shock, heart failure, and major bleeding
Almendro-Delia (2024)	Spain	Registry-based cohort	1,624	1,033 / 591	mixed P2Y12 inhibitors; NR	P2Y12 pretreatment before angiography or catheterization-laboratory arrival	P2Y12 administration in the catheterization laboratory	30 days	30-day MACE, NACE, bleeding, mortality, recurrent MI, stent thrombosis, and stroke
Danchin (2018)	France	Nationwide registry cohort	2,816-3,548	1,427-1,563 / 1,389-1,985	mixed P2Y12 inhibitors as part of dual antiplatelet therapy; NR	prehospital dual antiplatelet therapy with aspirin plus a P2Y12 inhibitor	no prehospital dual antiplatelet therapy; antiplatelet loading administered in-hospital according to care pathway	in-hospital to 1 year	mortality, recurrent MI, stroke, cardiogenic shock, MACE, and bleeding
de Waha (2014)	Germany	Observational cohort/post-hoc CMR analysis	423	84 / 339	clopidogrel; NR	upstream clopidogrel before catheterization-laboratory arrival	no upstream clopidogrel	acute/procedural	post-PCI TIMI 3 flow and CMR-derived reperfusion outcomes
Ducci (2013)	Italy	Randomized controlled trial	168	112 / 56	clopidogrel; 600 or 900 mg prehospital arms	prehospital clopidogrel 600 or 900 mg	peri-interventional clopidogrel 300 mg	procedural/in-hospital	post-PCI TIMI flow, no-reflow, and major bleeding
Dörler (2011)	Austria	Austrian acute PCI registry	5,356-5,955	1,498-1,635 / 3,858-4,320	clopidogrel; NR	clopidogrel pretreatment before arrival at the PCI centre	clopidogrel given later or no pretreatment before arrival at the PCI centre	procedural/in-hospital	pre-PCI and post-PCI TIMI flow, no-reflow, mortality, recurrent MI, stroke, and major bleeding
Elhadad (2025)	France	ACTION-SHOCK observational cohort with inverse-probability weighting	316 STEMI subgroup (421 overall AMI-CS)	197 / 119	mixed P2Y12 inhibitors; loading dose before angiography; exact dose NR	oral P2Y12 inhibitor loading before coronary angiography	no P2Y12 pretreatment before coronary angiography	procedural/in-hospital	pre-PCI and post-PCI TIMI flow, recurrent MI, stent thrombosis, mortality, MACE, stroke, and major bleeding
Fabris (2022)	Italy	Observational before-after cohort	537	237 / 300	ticagrelor 180 mg plus aspirin and heparin protocol at first medical contact	first-medical-contact or ambulance antithrombotic pretreatment before catheterization laboratory	aspirin-only first-medical-contact protocol with cath-lab/in-hospital P2Y12 management	procedural to 30 days	pre-PCI TIMI flow, mortality, recurrent MI, stent thrombosis, and any bleeding
Fefer (2009)	Canada	Retrospective observational cohort	383	217 / 166	clopidogrel; 300 or 600 mg	clopidogrel loading before primary PCI	clopidogrel loading after primary PCI	30 days	stent thrombosis, mortality, MACE, and major bleeding

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Gallo (2025)	Italy	Observational registry cohort with inverse-probability weighting	900-1,004	286-301 / 614-703	mixed P2Y12 inhibitors; NR	P2Y12 inhibitor before coronary angiography	no P2Y12 pretreatment before angiography	procedural/in-hospital	post-PCI TIMI 3 flow, stent thrombosis, and BARC major bleeding
Koul (2011)	Sweden	SCAAR registry cohort	13,847	9,813 / 4,034	clopidogrel; NR	upstream clopidogrel before primary PCI	no upstream clopidogrel before primary PCI	1 year	1-year mortality, recurrent MI, and related clinical outcomes
Koul (2018)	Sweden	SWEDEHEART/SCAAR registry cohort	7,433	5,438 / 1,995	ticagrelor; dose NR	ticagrelor pretreatment before arrival at the catheterization laboratory	ticagrelor administered in the catheterization laboratory	30 days	30-day composite of death, MI, and definite stent thrombosis (unique endpoint only; overlapping component outcomes excluded)
Kovacevic (2025)	Serbia	Retrospective observational single-center conference abstract	6,239	5,168 / 1,071	mixed P2Y12 inhibitors; potent agents in 63.6%; dose NR	P2Y12 inhibitor pretreatment before primary PCI	no P2Y12 inhibitor pretreatment	in-hospital and 30 days	baseline TIMI 3 flow, in-hospital mortality, and 30-day mortality; event counts reconstructed from reported percentages and denominators
Larson (2010)	United States	Regional STEMI network cohort	1,298-1,862	799-1,335 / 499-527	clopidogrel; 600 mg	longer pretreatment interval after loading at the presenting hospital	shorter pretreatment interval/direct PCI-hospital pathway	procedural to 1 year	pre-PCI TIMI flow, mortality, recurrent MI, stent thrombosis, stroke, MACE, and bleeding
Lev (2008)	Israel	Prospective registry/cohort	292	165 / 127	clopidogrel; 300-600 mg	clopidogrel preloading before PCI	clopidogrel loading immediately after or around PCI	30 days and 6 months	no-reflow, recurrent MI, stent thrombosis, mortality, and MACE
Lupi (2016)	Italy	Prospective observational cohort	286	143 / 143	ticagrelor; 180 mg	ticagrelor in ambulance or spoke hospital before transfer	ticagrelor at hub hospital/catheterization laboratory	procedural/in-hospital	pre-PCI and post-PCI TIMI flow, no-reflow, mortality, recurrent MI, stent thrombosis, stroke, and bleeding
Montalescot (2014)	International	Randomized double-blind trial	1,544-1,858	760-908 / 784-952	ticagrelor; 180 mg	prehospital ticagrelor loading	in-hospital/cath-lab ticagrelor loading	procedural and 30 days	pre-PCI and post-PCI TIMI flow, recurrent MI, stent thrombosis, mortality, MACE, stroke, and major bleeding
Moura Guedes (2020)	Portugal	Registry cohort	4,123	2,774 / 1,349	mixed P2Y12 inhibitors; NR	P2Y12 loading before coronary angiography/primary PCI	loading during or after angiography/primary PCI	in-hospital	mortality, recurrent MI, MACE, stroke, and major/any bleeding
Pepe (2018)	Italy	Multicenter registry cohort; multi-arm exposure	328	166 combined pretreatment arms / 162 comparator	ticagrelor or prasugrel; contemporary loading doses	P2Y12 loading before pPCI in two time strata	P2Y12 loading at pPCI/periangiography	procedural to 30 days	pre-PCI and post-PCI TIMI flow, recurrent MI, stent thrombosis, mortality, MACE, stroke, and major bleeding

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Postma (2014)	Netherlands	Prospective registry/before-after cohort	2,164-2,441	1,149-1,364 / 1,015-1,096	clopidogrel; 600 mg	ambulance administration of high-dose clopidogrel	in-hospital administration during or after PCI	procedural to 1 year	pre-PCI TIMI flow, mortality, recurrent MI, MACE, and major bleeding
Qadeer (2026)	United States	Retrospective EHR cohort with propensity matching	3,009-43,381, outcome-specific	853-21,489 / 2,156-24,000, outcome-specific	mixed oral P2Y12 inhibitors; dose NR	P2Y12 inhibitor before primary PCI	no pretreatment before primary PCI	30 days to 1 year	mortality, recurrent MI, stent thrombosis, MACE, stroke, and major bleeding
Redfors (2019)	Sweden	SCAAR registry cohort	44,804	37,840 / 6,964	mixed P2Y12 inhibitors; NR	pretreatment before primary PCI	no pretreatment before primary PCI	30 days	mortality and stent thrombosis
Rohla (2024)	Switzerland	Prospective Bern-PCI registry cohort	1,506 actual-treatment comparison	708 / 798	mixed P2Y12 inhibitors; ticagrelor/prasugrel predominant	actual P2Y12 pretreatment before angiography	no pretreatment; loading after anatomy known	30 days	recurrent MI, stent thrombosis, mortality, MACE, stroke, and major bleeding
Tohamy (2026)	Egypt	Prospective observational cohort	350	179 / 171	ticagrelor; 180 mg	prehospital loading >60 minutes before PPCI	cath-lab loading <60 minutes before PPCI	procedural to 6 months	pre-PCI and post-PCI TIMI flow, no-reflow, mortality, recurrent MI, stent thrombosis, MACE, and bleeding
Yudi (2018)	Australia	Registry-based cohort	2,705-3,237	855-1,030 / 1,850-2,207	mixed P2Y12 inhibitors; clopidogrel predominant	P2Y12 inhibitor before cath-lab arrival	P2Y12 inhibitor during or after PCI	procedural to 1 year	pre-PCI/post-PCI TIMI flow, no-reflow, mortality, recurrent MI, stent thrombosis, MACE, stroke, cardiogenic shock, and bleeding
Zeymer (2012)	Germany/Austria/Europe	Randomized controlled trial	280-337	131-166 / 149-171, outcome-specific	clopidogrel; 600 mg	prehospital clopidogrel loading	clopidogrel after diagnostic angiography	procedural/in-hospital	pre-PCI and post-PCI TIMI flow, mortality, recurrent MI, MACE, stroke, and TIMI major bleeding

NR: not reported; PreT: pre-treatment; PCI: percutaneous coronary intervention; MI: myocardial infarction; MACE: Major adverse cardiovascular events; NACE: Net adverse clinical events; TIMI: thrombolysis in myocardial infarction; CMR: Cardiovascular magnetic resonance imaging; STEMI: ST-segment elevation myocardial infarction; AMI-CS: Acute myocardial infarction complicated by cardiogenic shock; BARC: Bleeding Academic Research Consortium; EHR: electronic health record; SCAAR: Swedish Coronary Angiography and Angioplasty registry. All 26 studies contributed to at least one eligible pooled outcome. When denominators varied by outcome, the analytical range used in the final dataset is shown rather than a single article-level total. For overlapping registries, only nonoverlapping outcome data were retained within each meta-analysis.

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Table 2. Subgroup analyses and between-subgroup meta-regression results

Outcome	Odds ratio (95% CI)	p for effect	I^2 (p heterogeneity)
Overall pretreatment			
Pre-PCI TIMI 3 flow			
P2Y12 inhibitor group (p=0.289 for interaction)			
Mixed P2Y12 inhibitors (k=3)	1.29 (1.01-1.66)	0.045	36.6% (p=0.206)
Ticagrelor (k=4)	1.95 (1.05-3.63)	0.035	84.4% (p<0.001)
Post-PCI TIMI 3 flow			
Study design (p=0.883 for interaction)			
Observational (k=7)	1.11 (0.72-1.70)	0.631	75.7% (p<0.001)
RCT (k=3)	1.11 (0.88-1.41)	0.391	0.0% (p=0.849)
P2Y12 inhibitor group (p=0.357 for interaction)			
Clopidogrel (k=4)	1.33 (1.11-1.58)	0.002	0.0% (p=0.746)
Mixed P2Y12 inhibitors (k=4)	0.89 (0.44-1.76)	0.729	79.8% (p=0.002)
In-hospital recurrent MI / re-infarction			
P2Y12 inhibitor group (p=0.003 for interaction)			
Clopidogrel (k=3)	0.37 (0.22-0.62)	<0.001	0.0% (p=0.785)
Mixed P2Y12 inhibitors (k=3)	2.52 (0.62-10.29)	0.198	63.6% (p=0.064)
30-day recurrent MI / re-infarction			
P2Y12 inhibitor group (p<0.001 for interaction)			
Clopidogrel (k=3)	0.36 (0.22-0.60)	<0.001	0.0% (p=0.553)
Mixed P2Y12 inhibitors (k=5)	0.95 (0.81-1.12)	0.543	0.0% (p=0.971)
30-day stent thrombosis			
P2Y12 inhibitor group (p=0.019 for interaction)			
Clopidogrel (k=3)	0.30 (0.15-0.60)	<0.001	0.0% (p=0.779)
Mixed P2Y12 inhibitors (k=5)	1.12 (0.58-2.18)	0.738	79.5% (p<0.001)
In-hospital all-cause mortality			
P2Y12 inhibitor group (p=0.718 for interaction)			
Clopidogrel (k=5)	0.64 (0.47-0.87)	0.004	22.3% (p=0.272)
Mixed P2Y12 inhibitors (k=5)	0.91 (0.56-1.49)	0.712	84.7% (p<0.001)
Ticagrelor (k=3)	0.71 (0.22-2.27)	0.563	60.3% (p=0.081)

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30-day all-cause mortality			
P2Y12 inhibitor group (p=0.175 for interaction)			
Clopidogrel (k=4)	1.14 (0.82-1.59)	0.427	0.0% (p=0.731)
Mixed P2Y12 inhibitors (k=9)	0.78 (0.59-1.03)	0.076	90.2% (p<0.001)
Major bleeding - in-hospital/discharge			
P2Y12 inhibitor group (p=0.059 for interaction)			
Clopidogrel (k=7)	0.89 (0.73-1.08)	0.223	0.0% (p=0.751)
Mixed P2Y12 inhibitors (k=5)	1.27 (0.90-1.78)	0.171	36.7% (p=0.177)
Bleeding definition (p=0.150 for interaction)			
BARC (k=3)	1.43 (0.56-3.67)	0.454	46.0% (p=0.157)
TIMI (k=5)	0.96 (0.69-1.33)	0.810	0.0% (p=0.602)
Study-defined/unclear (k=6)	0.95 (0.80-1.14)	0.578	0.0% (p=0.645)

BARC: Bleeding Academic Research Consortium; CI: confidence interval; MI: myocardial infarction; OR: odds ratio; RCT: randomized controlled trial; TIMI: Thrombolysis in Myocardial Infarction. Interaction p values are from categorical between-subgroup meta-regression. Subgroup estimates were reported only when the predefined minimum number of independent studies was met.

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Table 3: Domain-level risk-of-bias assessment of randomized trials

Study	D1 Randomization	D2 Deviations	D3 Missing data	D4 Measurement	D5 Reporting	Overall	Rationale
Ducci (2013)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	Small randomized study with limited detail on concealment/blinding; comparator dose differed from intervention strategy, and angiographic outcomes may be sensitive to open-label care pathways.
Montalescot (2014)	Low	Low	Low	Low	Low	Low	Large, randomized, double-blind placebo-controlled trial with objective clinical and angiographic outcomes and complete reporting; judged as low risk overall.
Zeymer (2012)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Randomized trial but small sample and limited publicly extractable detail on allocation/concealment and selective reporting; open-label/periprocedural timing may affect deviations, while outcomes were largely objective.

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Table 4: ROBINS-I assessment for nonrandomized studies

Study	D1 Confounding	D2 Selection	D3 Classification	D4 Deviations	D5 Missing data	D6 Measurement	D7 Reporting	Overall	Rationale
Alexander (2008)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Large registry; nonrandomized upstream treatment was strongly linked to care pathway and co-interventions.
Almendro-Delia (2024)	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Large modern registry with adjusted analyses; residual treatment-selection and system-of-care confounding remain.
Danchin (2018)	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Prospective national registry with adjustment; residual confounding persists, but exposure and outcome ascertainment were relatively robust.
de Waha (2014)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Small nonrandomized cohort; treatment timing may be associated with baseline risk and care-pathway factors.
Dörler (2011)	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Large registry with objective outcomes; residual confounding remains.
Elhadad (2025)	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	AMI-CS observational cohort using inverse-probability weighting; STEMI subgroup relied partly on supplementary data and residual confounding by shock severity and treatment selection remains important.
Fabris (2022)	Serious	Moderate	Moderate	Serious	Moderate	Low	Moderate	Serious	Before-after regional protocol study; exposure combined ticagrelor with aspirin/heparin first-medical-contact treatment, making timing and co-intervention effects difficult to isolate.
Fefer (2009)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Residual confounding and treatment selection were likely; timing groups may reflect clinical logistics and operator strategy.
Gallo (2025)	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Contemporary real-world analysis; residual confounding remains, but the timing definition was directly relevant.
Koul (2011)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Large registry with residual confounding by treatment pathway and potential cohort-overlap concerns.
Koul (2018)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Registry-based timing comparison with residual confounding and overlapping SCAAR population; only the unique composite outcome was retained.

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Kovacevic (2025)	Serious	Moderate	Moderate	Moderate	Serious	Low	Serious	Serious	Single-center retrospective conference abstract with limited adjustment, nonrandomized treatment timing, reconstructed event counts, and incomplete domain-level reporting.
Larson (2010)	Serious	Moderate	Serious	Moderate	Moderate	Low	Moderate	Serious	Exposure partly reflected transfer pathway and pretreatment duration rather than a clean prehospital versus in-hospital contrast.
Lev (2008)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Nonrandomized timing with likely confounding by clinical stability, transfer pathway, and treatment selection.
Lupi (2016)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Timing was strongly linked to transport distance and referral pathway.
Moura Guedes (2020)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Nonrandomized timing decision with likely residual confounding and pathway effects.
Pepe (2018)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Timing categories may be confounded by referral delay and clinical logistics; multi-arm data required combination to avoid shared-comparator duplication.
Postma (2014)	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate	Moderate	Clear ambulance versus hospital timing with objective outcomes; nonrandomized before-after allocation remains a limitation.
Qadeer (2026)	Serious	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Administrative/EHR data with outcome-specific denominators; misclassification and residual confounding remain despite matching.
Redfors (2019)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Very large registry with objective endpoints but nonrandomized treatment and potential cohort overlap.
Rohla (2024)	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate	Moderate	Modern cohort with a clear timing contrast and objective outcomes; residual confounding remains.
Tohamy (2026)	Serious	Moderate	Moderate	Moderate	Serious	Low	Moderate	Serious	Single-center nonrandomized timing comparison with possible incomplete data and reporting concerns.
Yudi (2018)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Observational cath-lab timing comparison with residual confounding and treatment-selection bias.

ROBINS-I: Risk of Bias In Non-randomized Studies of Interventions; RoB 2: revised Cochrane risk-of-bias tool for randomized trials; AMI-CS: Acute myocardial infarction complicated by cardiogenic shock; EHR: electronic health record. RoB 2 domains: D1: randomization process; D2: deviations from intended interventions; D3: missing outcome data; D4: outcome measurement; D5: selection of the reported result. ROBINS-I domains: D1: confounding; D2: participant selection; D3: intervention classification; D4: deviations from intended interventions; D5: missing data; D6: outcome measurement; D7: selection of the reported result.

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Table 5: GRADE assessment of all pooled outcome-time strata in the broad and direct prehospital analyses

Outcome and time point	Studies (k)	OR (95% CI)	P value	I^2	Certainty	GRADE considerations
Broad pretreatment vs delayed/no pretreatment						
Angiographic and reperfusion outcomes						
Pre-PCI TIMI 2/3 flow	8	1.37 (1.03 to 1.83)	0.032	87.5%	⊕◯◯◯ Very low	Predominantly nonrandomized evidence; serious RoB; very serious inconsistency; indirectness from variable timing; nominal significance was not retained with Knapp–Hartung adjustment and was unstable to several leave-one-out exclusions.
Pre-PCI TIMI 3 flow	9	1.39 (1.03 to 1.88)	0.029	83.5%	⊕◯◯◯ Very low	Predominantly nonrandomized evidence; serious RoB; very serious inconsistency; indirectness from variable timing; nominal significance was not retained with Knapp–Hartung adjustment and was lost after exclusion of reconstructed Kovacevic data.
Post-PCI TIMI 3 flow	10	1.09 (0.82 to 1.44)	0.569	73.9%	⊕◯◯◯ Very low	Serious RoB; serious inconsistency; indirectness; imprecision; no detected small-study effect.
No-reflow	7	0.75 (0.53 to 1.06)	0.105	38.9%	⊕◯◯◯ Very low	Serious RoB; indirectness; imprecision; publication bias not assessable.
Thirty-day clinical outcomes						
Recurrent MI / re-infarction	10	0.70 (0.50 to 0.96)	0.029	40.0%	⊕◯◯◯ Very low	Serious RoB; indirectness; possible small-study effects (Egger p=0.079); primary significance was not stable to omission of Larson or Postma; multiplicity.
Stent thrombosis	10	0.65 (0.36 to 1.18)	0.156	76.7%	⊕◯◯◯ Very low	Serious RoB; very serious inconsistency; indirectness; imprecision; possible small-study effects by Begg test.
All-cause mortality	15	0.91 (0.72 to 1.14)	0.397	84.6%	⊕◯◯◯ Very low	Serious RoB; very serious inconsistency; indirectness; imprecision; no detected small-study effect.
MACE / MACCE	9	0.90 (0.73 to 1.10)	0.299	80.3%	⊕◯◯◯ Very low	Serious RoB; very serious inconsistency; variable composite definitions; imprecision; publication bias not assessable.
Stroke	6	0.69 (0.56 to 0.85)	<0.001	0.0%	⊕◯◯◯ Very low	Predominantly nonrandomized evidence with serious RoB; indirectness; publication bias not assessable; Knapp–Hartung significance retained but the estimate became null after exclusion of Qadeer, which carried most of the weight.
In-hospital/discharge clinical outcomes						
Recurrent MI / re-infarction	7	0.94 (0.39 to 2.26)	0.889	72.3%	⊕◯◯◯ Very low	Serious RoB; serious inconsistency; indirectness; very serious imprecision; publication bias not assessable.
Stent thrombosis	5	1.03 (0.54 to 1.95)	0.932	5.6%	⊕◯◯◯ Very low	Serious RoB; few events; very serious imprecision; indirectness; publication bias not assessable.
All-cause mortality	13	0.81 (0.59 to 1.10)	0.176	72.1%	⊕◯◯◯ Very low	Serious RoB; serious inconsistency; indirectness; imprecision; no detected small-study effect.
MACE / MACCE	4	0.94 (0.60 to 1.48)	0.799	73.3%	⊕◯◯◯ Very low	Serious RoB; serious inconsistency; variable composite definitions; imprecision; publication bias not assessable.
Stroke	6	0.93 (0.57 to 1.52)	0.764	24.4%	⊕◯◯◯ Very low	Serious RoB; sparse events; indirectness; imprecision; publication bias not assessable.
Cardiogenic shock	3	0.67 (0.53 to 0.85)	<0.001	0.0%	⊕◯◯◯ Very low	Only three nonrandomized studies; serious RoB; high susceptibility to reverse causation/confounding by indication; Knapp–Hartung CI crossed the null; publication bias not assessable.
Six-month clinical outcomes						

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All-cause mortality	3	1.18 (1.09 to 1.29)	<0.001	0.0%	⊕◯◯◯ Very low	Only three nonrandomized studies; serious RoB; temporally inconsistent mortality pattern; Qadeer contributed 99.6% of random-effects weight; Knapp–Hartung CI crossed the null; publication bias not assessable.
Recurrent MI / re-infarction	3	0.77 (0.65 to 0.91)	0.002	0.0%	⊕◯◯◯ Very low	Only three nonrandomized studies; serious RoB; indirectness; Qadeer contributed 97.8% of random-effects weight; Knapp–Hartung CI crossed the null; publication bias not assessable.
Stent thrombosis	3	0.53 (0.06 to 4.55)	0.563	66.0%	⊕◯◯◯ Very low	Only three nonrandomized studies; serious RoB; serious inconsistency; very serious imprecision; publication bias not assessable.
MACE / MACCE	3	0.89 (0.48 to 1.65)	0.704	74.3%	⊕◯◯◯ Very low	Only three nonrandomized studies; serious RoB; serious inconsistency; variable composite definitions; imprecision.
One-year clinical outcomes						
All-cause mortality	5	0.89 (0.71 to 1.11)	0.297	84.0%	⊕◯◯◯ Very low	Nonrandomized evidence with serious RoB; very serious inconsistency; indirectness; imprecision; publication bias not assessable.
Recurrent MI / reinfarction	5	0.79 (0.70 to 0.89)	<0.001	22.6%	⊕◯◯◯ Very low	Nonrandomized evidence with serious RoB and indirectness; publication bias not assessable; association remained significant with Knapp–Hartung adjustment and across leave-one-out analyses, but certainty remains very low.
MACE / MACCE	3	1.05 (0.91 to 1.22)	0.510	51.4%	⊕◯◯◯ Very low	Only three nonrandomized studies; serious RoB; serious inconsistency; variable composite definitions; imprecision.
Safety outcomes						
Major bleeding-in-hospital/discharge	14	1.05 (0.86 to 1.28)	0.655	24.3%	⊕◯◯◯ Very low	Serious RoB; indirectness from heterogeneous bleeding definitions; imprecision; no detected small-study effect.
Major bleeding-30 days	4	0.97 (0.85 to 1.12)	0.688	0.0%	⊕◯◯◯ Very low	Serious RoB; heterogeneous bleeding definitions; imprecision; publication bias not assessable.
Any bleeding-in-hospital/discharge	5	1.34 (0.85 to 2.11)	0.202	66.6%	⊕◯◯◯ Very low	Nonrandomized evidence with serious RoB; serious inconsistency; variable bleeding definitions; imprecision.
Direct prehospital vs in-hospital/Cath lab loading						
Angiographic and reperfusion outcomes						
Pre-PCI TIMI 2/3 flow	4	1.71 (1.21 to 2.41)	0.002	72.0%	⊕◯◯◯ Very low	Mixed randomized and nonrandomized evidence; serious RoB; serious inconsistency; sparse evidence; nominal significance was not retained with Knapp–Hartung adjustment.
Pre-PCI TIMI 3 flow	5	1.76 (1.08 to 2.89)	0.025	79.5%	⊕◯◯◯ Very low	Mixed randomized and nonrandomized evidence; serious RoB; very serious inconsistency; sparse evidence and imprecision; nominal significance was not retained with Knapp–Hartung adjustment.
Post-PCI TIMI 3 flow	3	1.17 (0.92 to 1.48)	0.197	0.0%	⊕◯◯◯ Very low	Only three studies; concerns about RoB in part of the evidence; imprecision; publication bias not assessable.
Thirty-day clinical outcomes						
Recurrent MI / reinfarction	3	0.52 (0.31 to 0.87)	0.012	0.0%	⊕◯◯◯ Very low	Only three studies with few events; serious RoB in nonrandomized evidence; sparse evidence; nominal significance was not retained with Knapp–Hartung adjustment; publication bias not assessable.
All-cause mortality	4	0.98 (0.55 to 1.75)	0.958	79.9%	⊕◯◯◯ Very low	Serious RoB; very serious inconsistency; very serious imprecision; sparse evidence.
In-hospital/discharge clinical outcomes						

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All-cause mortality	4	0.65 (0.27 to 1.56)	0.337	62.5%	⊕◯◯◯ Very low	Serious RoB; serious inconsistency; very serious imprecision; sparse evidence.
Safety outcomes						
Major bleeding-in-hospital/discharge	4	0.94 (0.63 to 1.41)	0.770	14.5%	⊕◯◯◯ Very low	Serious RoB; heterogeneous bleeding definitions; imprecision; sparse evidence; publication bias not assessable.

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; OR, odds ratio; RoB, risk of bias; TIMI, Thrombolysis in Myocardial Infarction. All ratings were very low (⊕◯◯◯). "Publication bias not assessable" indicates fewer than 10 independent studies. Outcome–time strata with fewer than three independent studies were not pooled. GRADE judgments are based on the primary REML estimates, with Knapp–Hartung and influence analyses used to inform imprecision and fragility considerations; detailed sensitivity results are in Supplementary Tables S2–S5.

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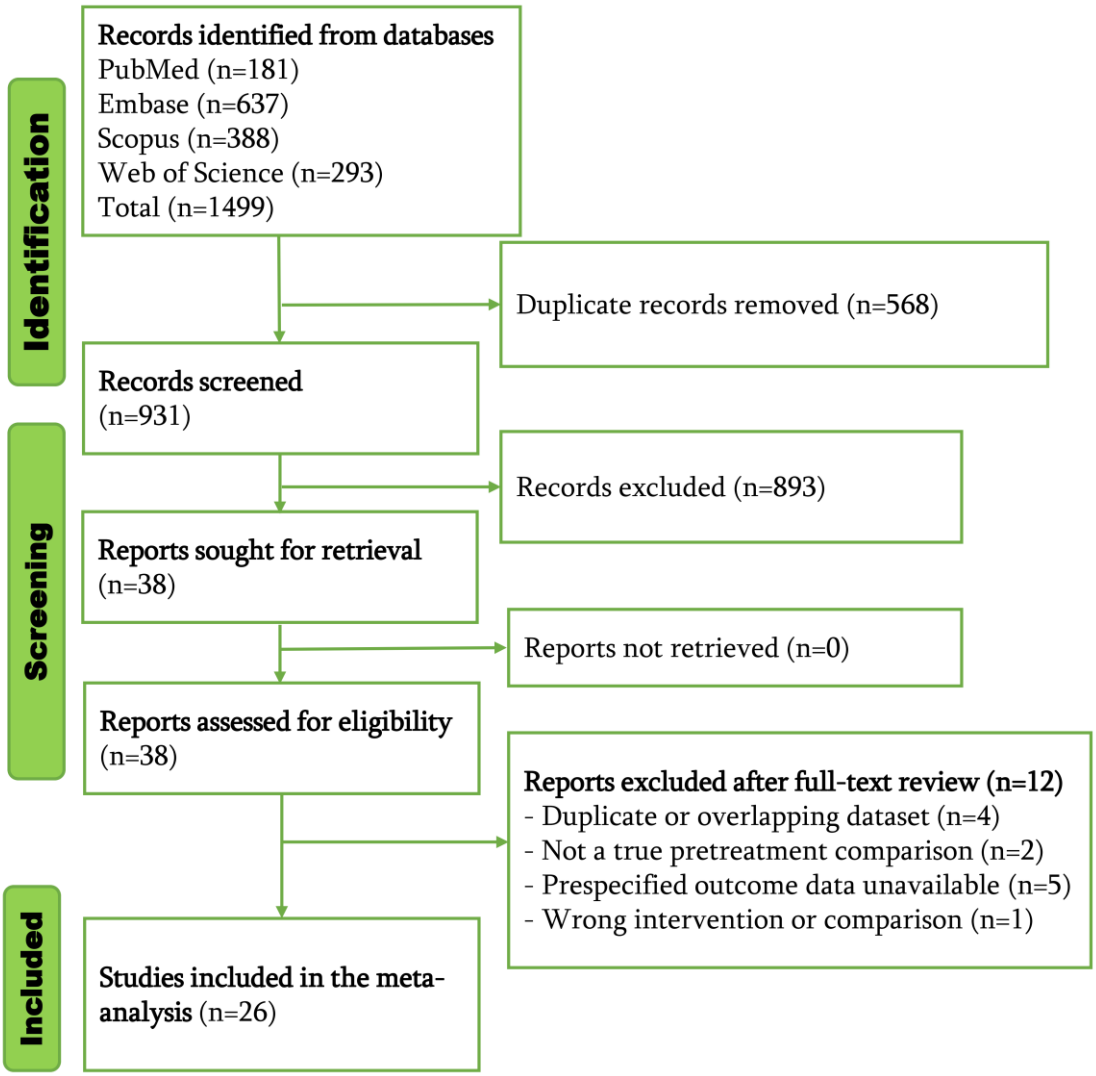


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram for identification, screening, eligibility assessment, and inclusion of studies evaluating the timing of oral P2Y12 loading in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

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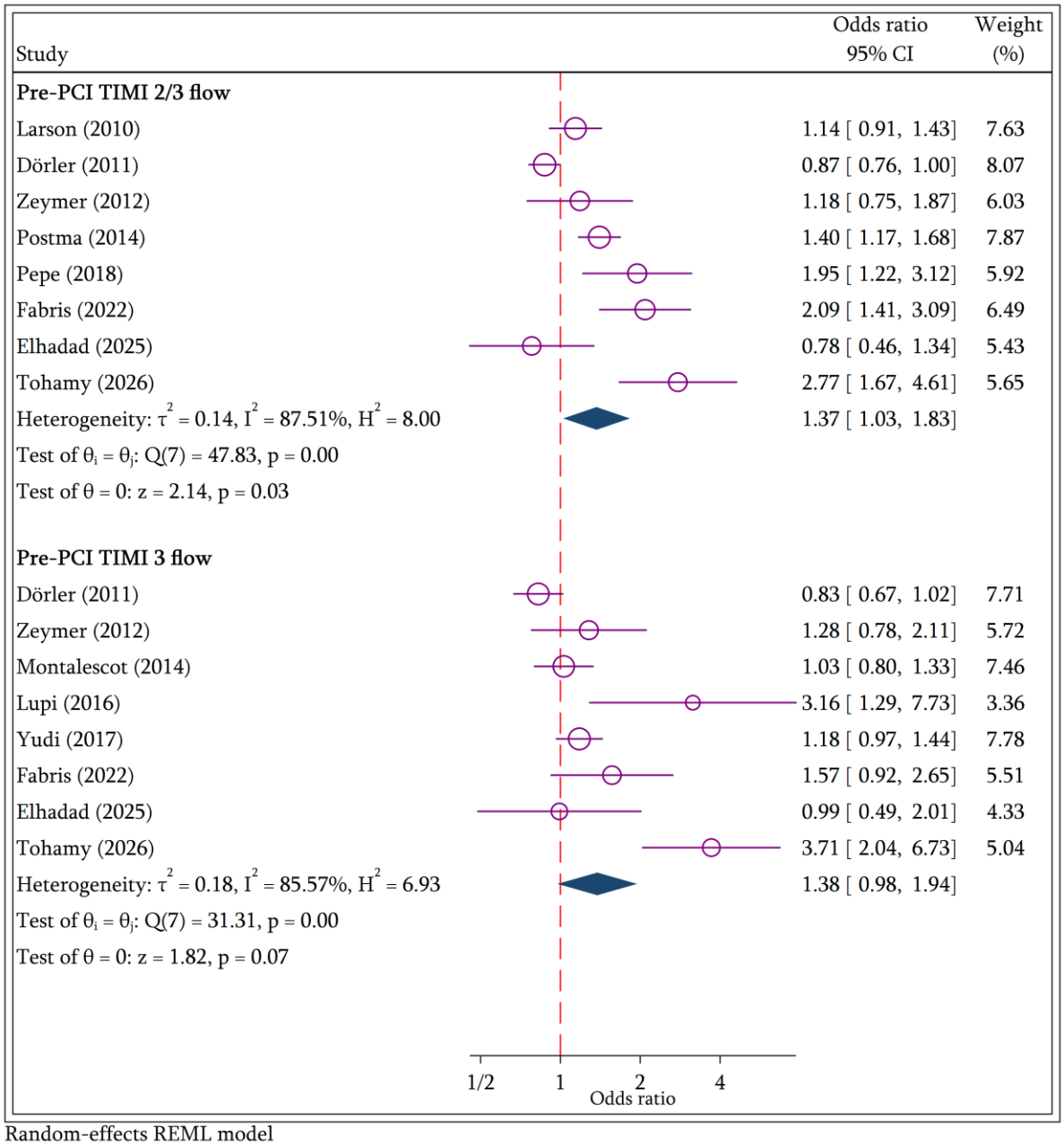


Figure 2: Pre-percutaneous coronary intervention (PCI) reperfusion outcomes in the broad pretreatment analysis. Study-specific odds ratios and 95% confidence intervals are shown separately for pre-PCI thrombolysis in myocardial infarction (TIMI) 2/3 flow and pre-PCI TIMI 3 flow. No pooled estimate was calculated across the two outcomes. REML: restricted maximum likelihood.

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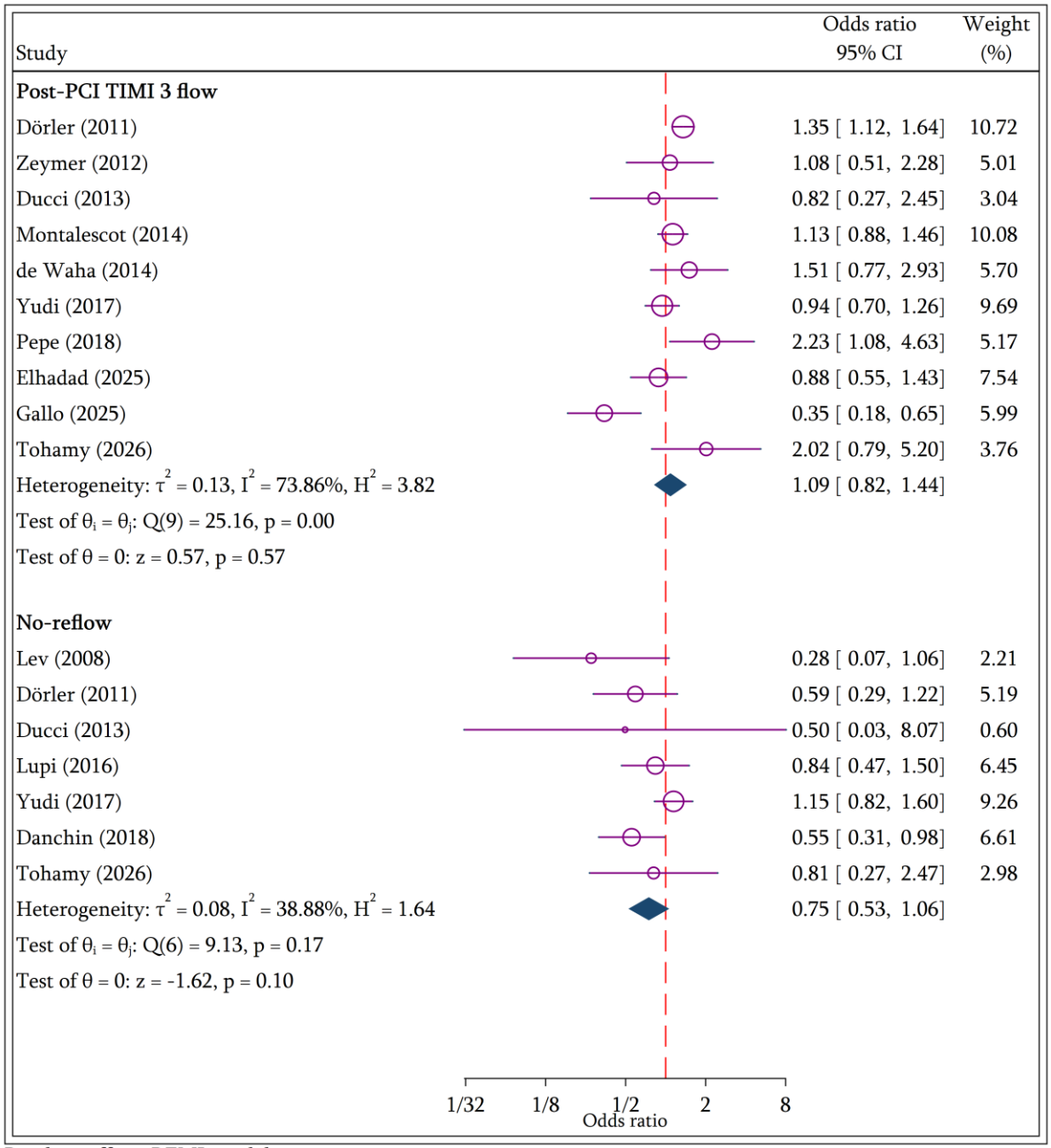


Figure 3: Post-percutaneous coronary intervention (PCI) and microvascular reperfusion outcomes in the broad pretreatment analysis. Study-specific odds ratios and 95% confidence intervals are shown separately for post-PCI thrombolysis in myocardial infarction (TIMI) 3 flow and no-reflow. No pooled estimate was calculated across outcomes. CI: confidence interval; REML: restricted maximum likelihood.

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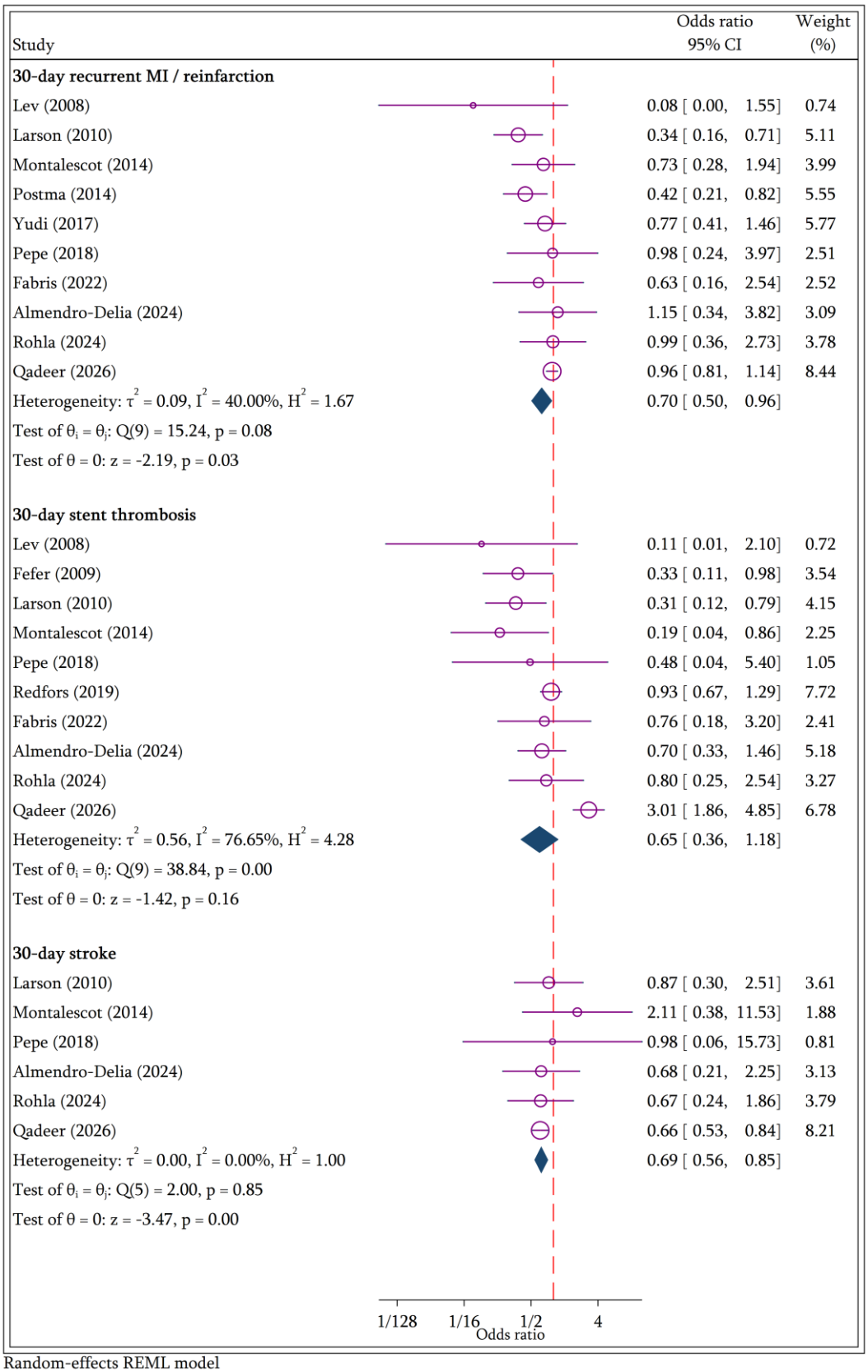


Figure 4: Thirty-day thrombotic and neurologic outcomes in the broad pretreatment analysis: recurrent myocardial infarction (MI) or reinfarction, stent thrombosis, and stroke. Outcomes were pooled separately. CI: confidence interval; REML: restricted maximum likelihood.

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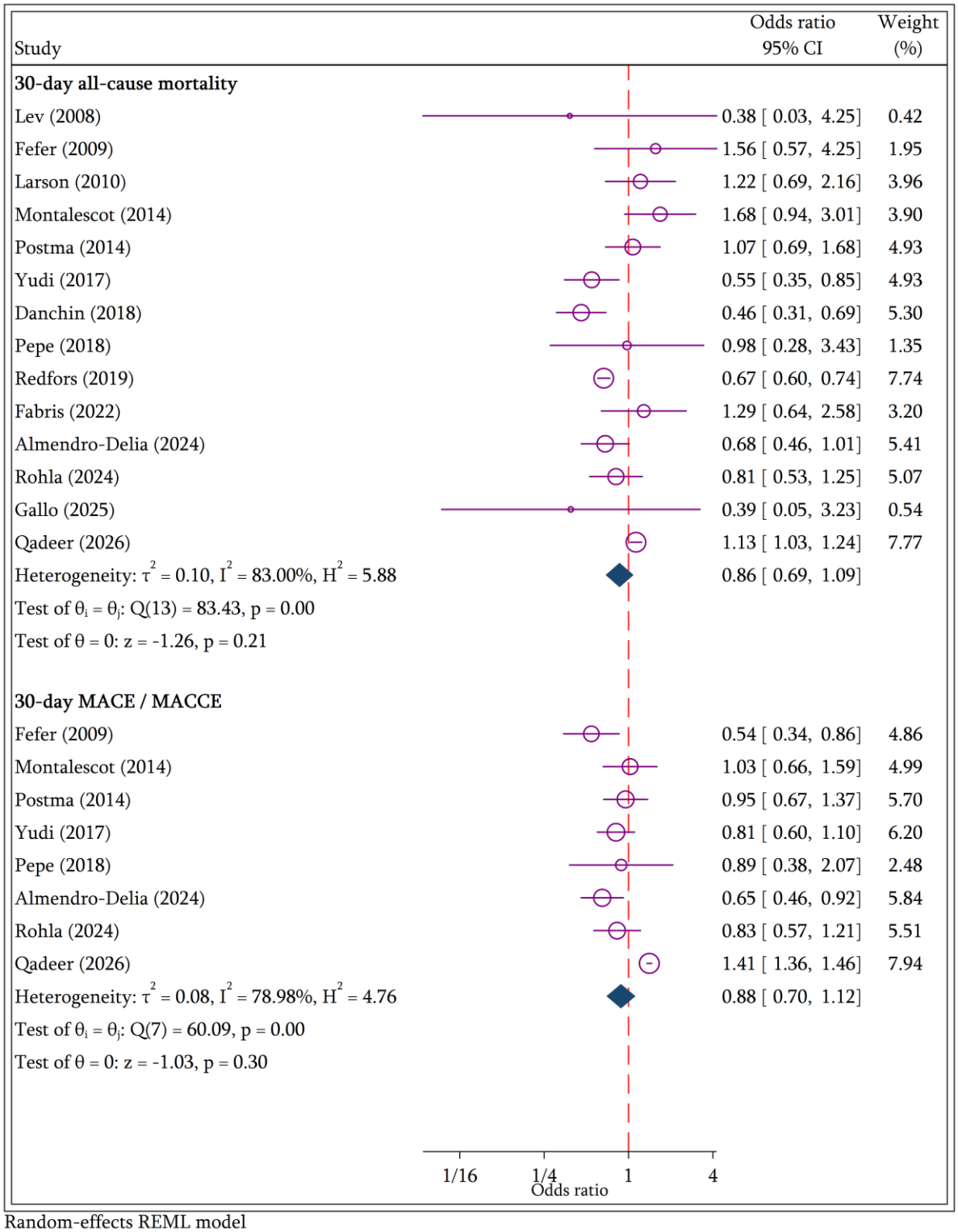


Figure 5: Thirty-day all-cause mortality and major adverse cardiac and cerebrovascular events (MACE/MACCE) in the broad pretreatment analysis. Separate outcome-specific random-effects estimates are shown. CI: confidence interval; REML: restricted maximum likelihood.

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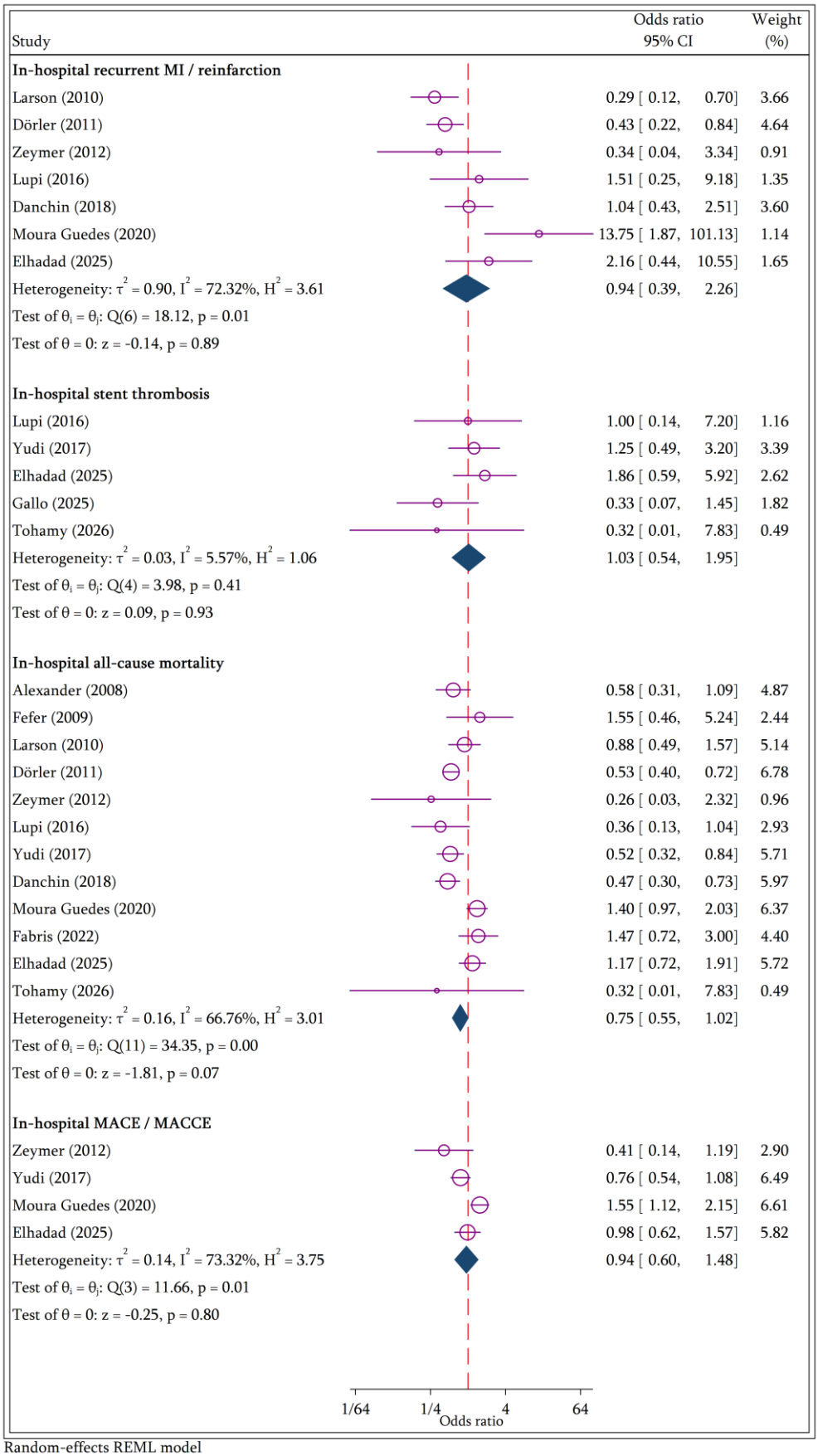


Figure 6: In-hospital ischemic outcomes in the broad pretreatment analysis: recurrent myocardial infarction (MI) or reinfarction, stent thrombosis, all-cause mortality, and major adverse cardiac and cerebrovascular events (MACE/MACCE). Outcomes were pooled separately. CI: confidence interval; REML: restricted maximum likelihood.

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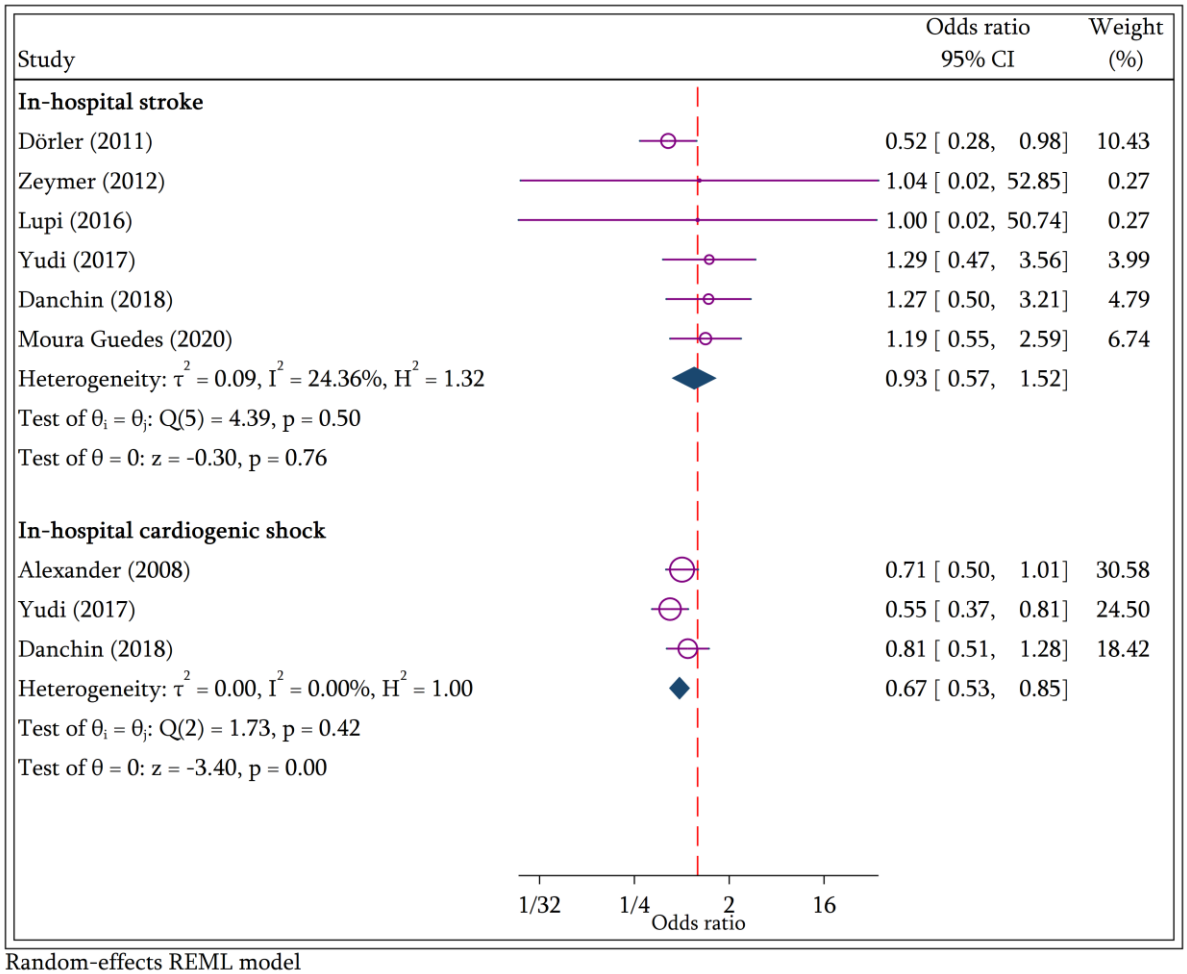


Figure 7: In-hospital stroke and cardiogenic shock in the broad pretreatment analysis. Separate outcome-specific estimates are shown. CI: confidence interval; REML: restricted maximum likelihood.

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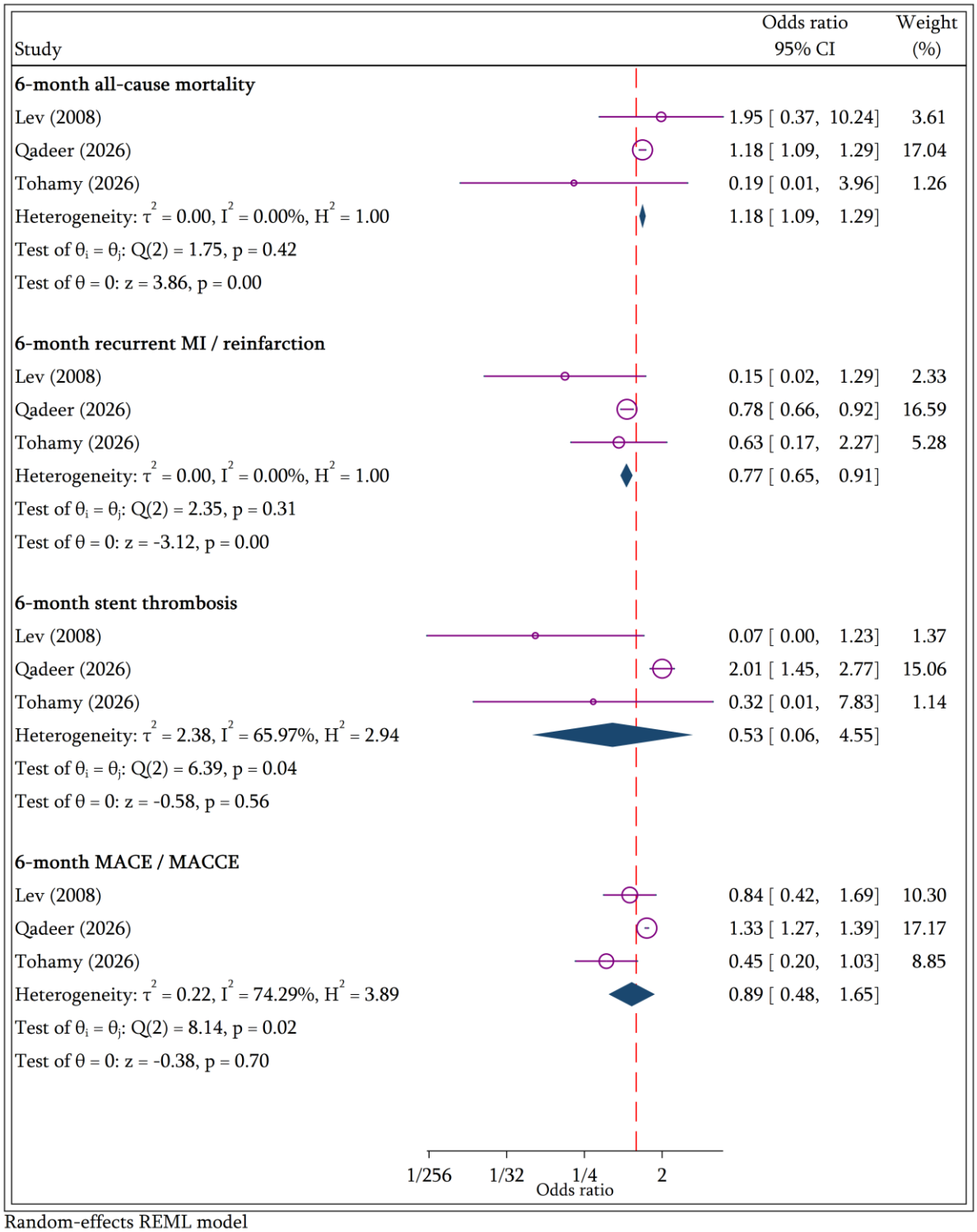


Figure 8: Six-month clinical outcomes in the broad pretreatment analysis: all-cause mortality, recurrent myocardial infarction (MI) or reinfarction, stent thrombosis, and major adverse cardiac and cerebrovascular events (MACE/MACCE). Outcomes were pooled separately. CI: confidence interval; REML: restricted maximum likelihood.

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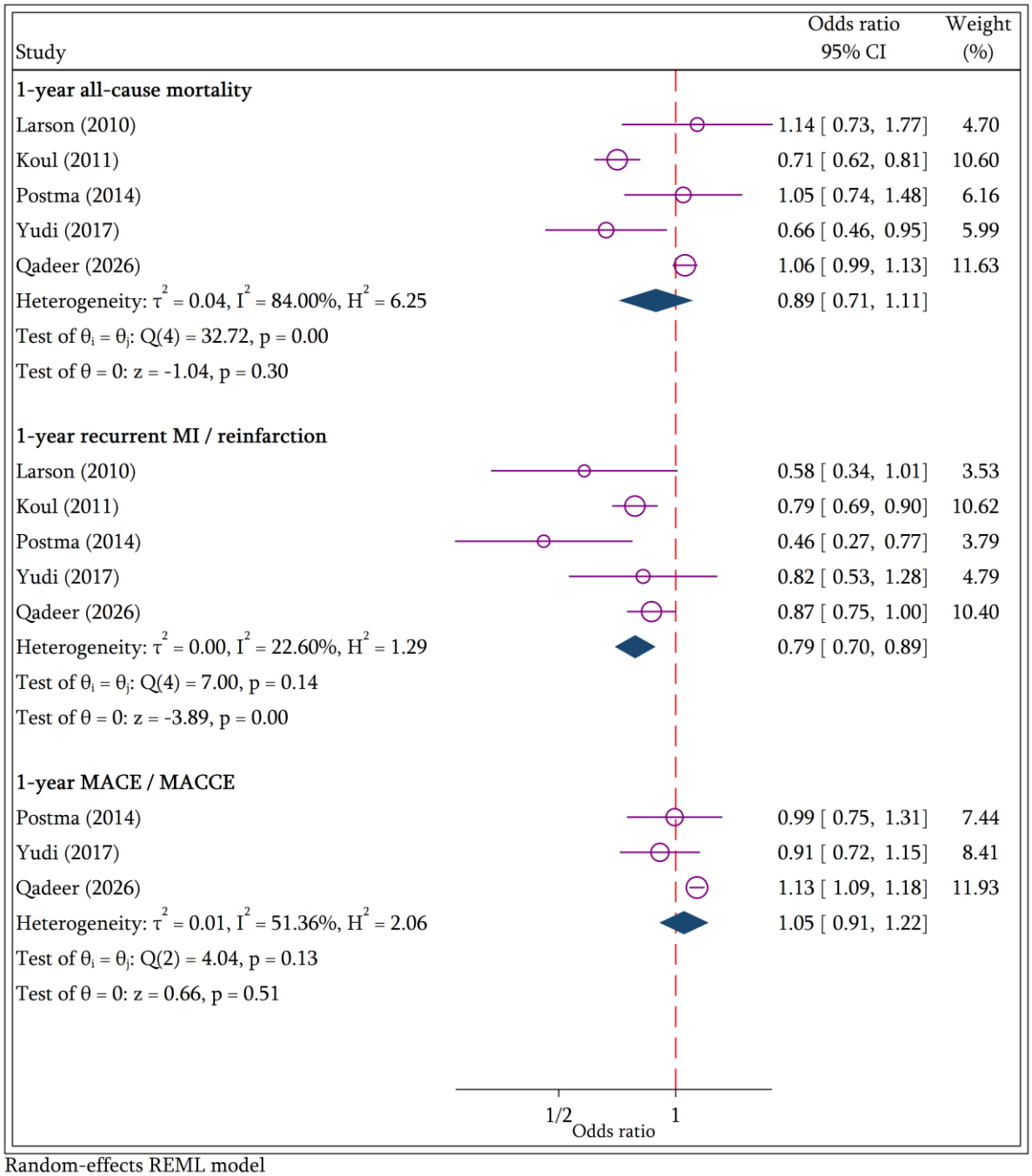


Figure 9: One-year clinical outcomes in the broad pretreatment analysis: all-cause mortality, recurrent myocardial infarction (MI) or reinfarction, and major adverse cardiac and cerebrovascular events (MACE/MACCE). Outcomes were pooled separately. CI: confidence interval; REML: restricted maximum likelihood.

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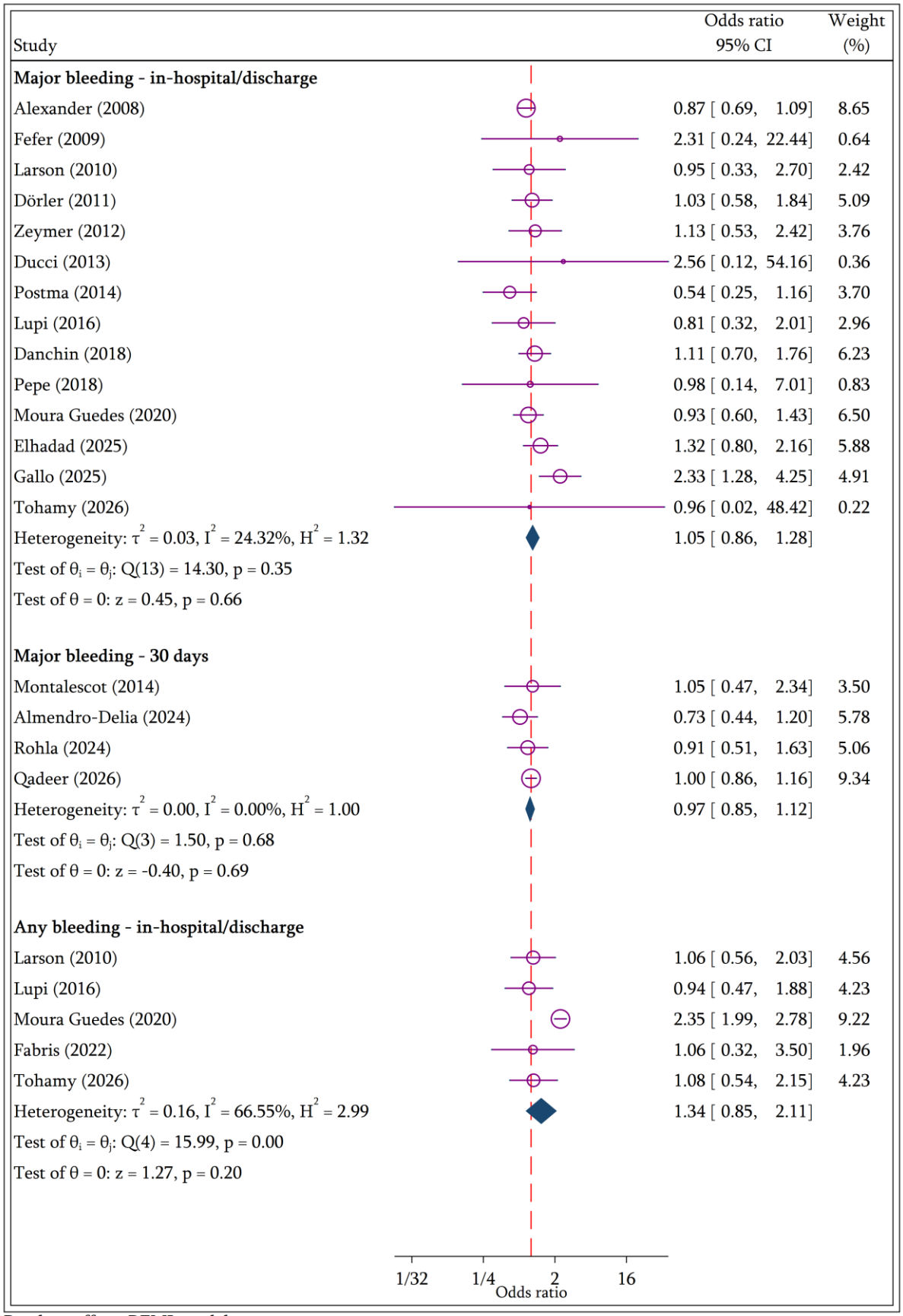


Figure 10: Bleeding outcomes in the broad pretreatment analysis: in-hospital/discharge major bleeding, 30-day major bleeding, and any in-hospital/discharge bleeding. Outcomes were pooled separately. CI: confidence interval; REML: restricted maximum likelihood. Supplementary Appendix 1: Full search strategy in different databases

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Appendix

Supplementary Appendix 1: Full search strategy in different databases

PubMed

```
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AND
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)
AND
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Embase

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AND
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 OR upstream:ti,ab,kw OR pretreat*:ti,ab,kw OR 'pre-treatment':ti,ab,kw OR pretreated:ti,ab,kw
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Scopus

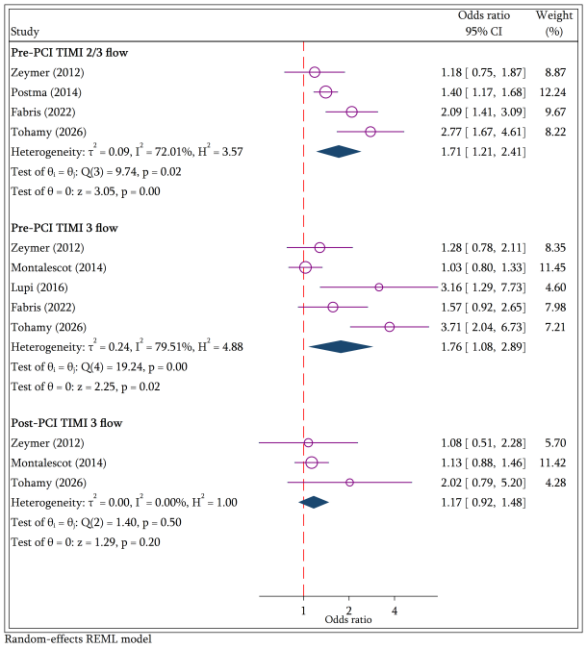
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 AND
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 )
 AND
 (
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 )
 AND
 (
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Web of Science Core Collection

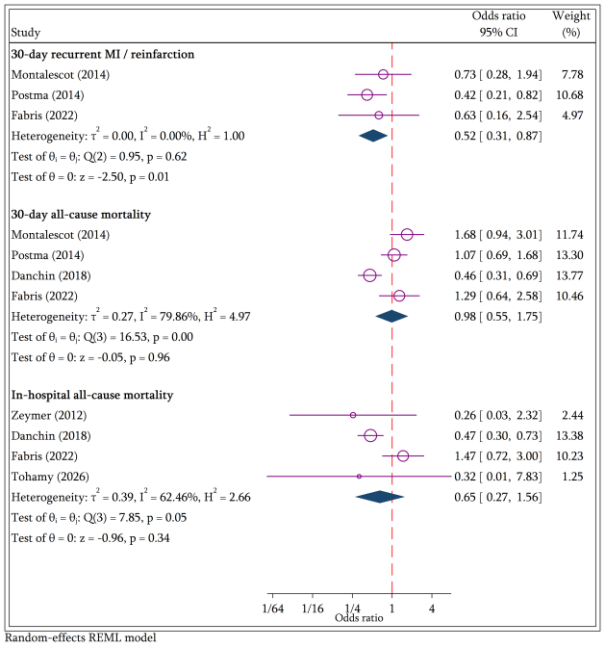
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 AND
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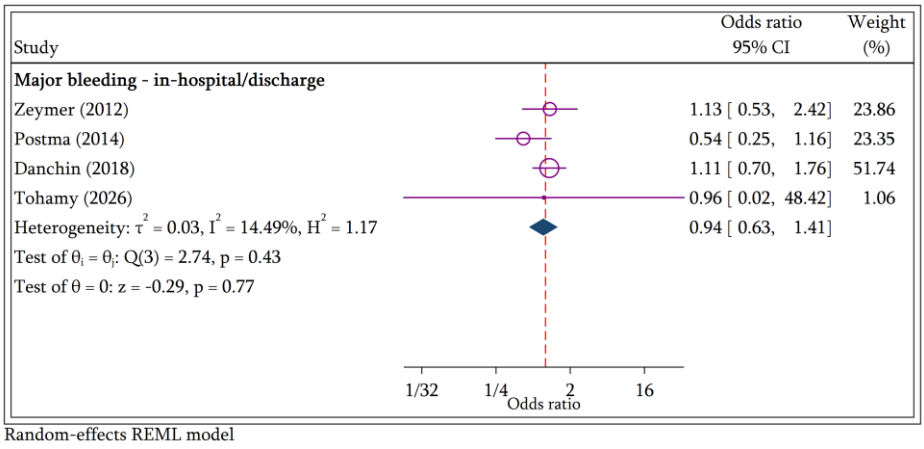
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S1



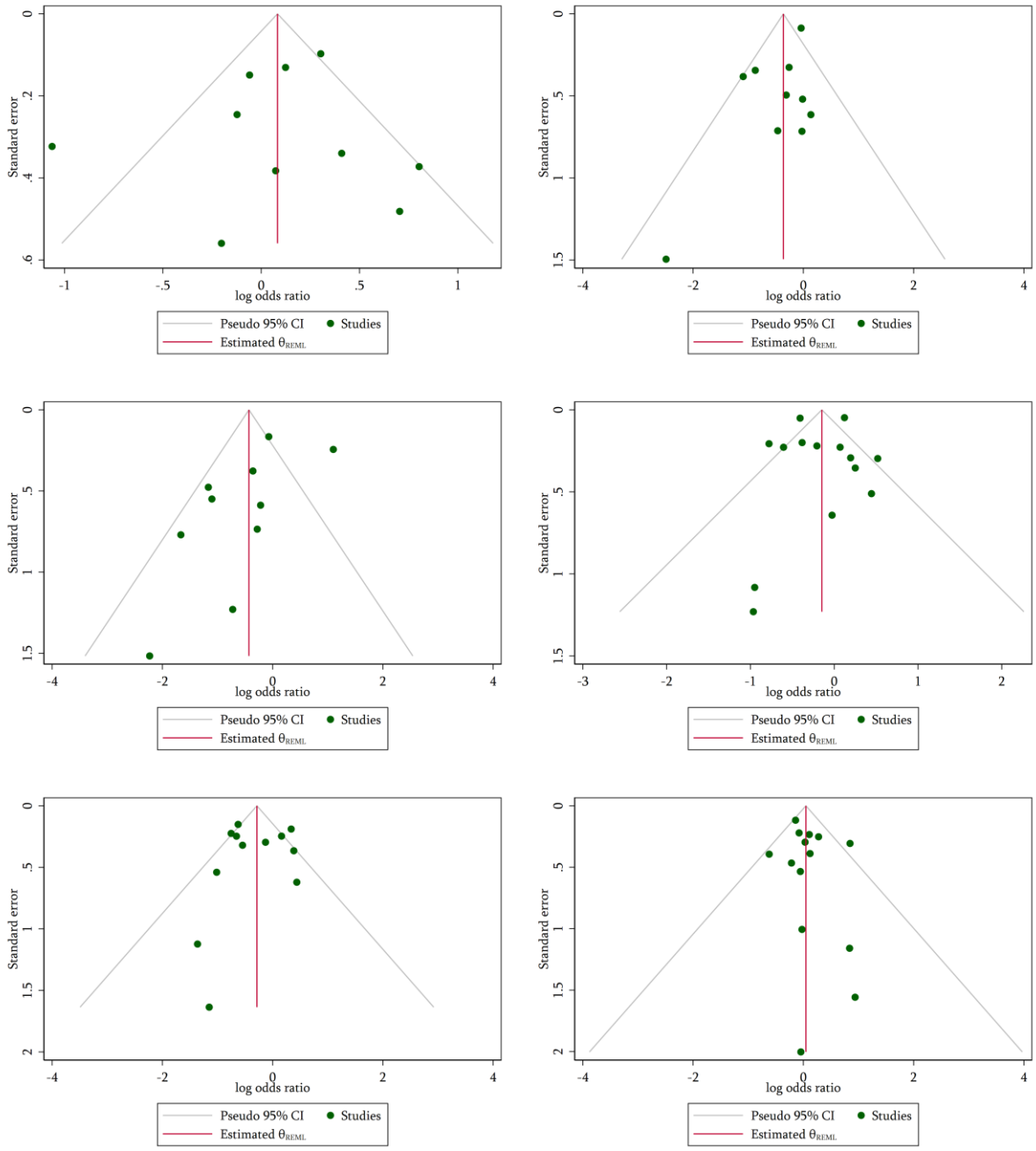
S2



S3

Supplementary Appendix 2: Prehospital versus in-hospital administration of P2Y12. S1: Reperfusion outcomes in the strict prehospital analysis. Prehospital loading was compared directly with in-hospital or catheterization-laboratory loading for pre-PCI TIMI 2/3 flow, pre-PCI TIMI 3 flow, and post-PCI TIMI 3 flow. S2: Clinical outcomes in the strict prehospital analysis: 30-day recurrent MI or reinfarction, 30-day all-cause mortality, and in-hospital all-cause mortality. S3: Major bleeding in the strict prehospital versus in-hospital or catheterization-laboratory analysis. CI: confidence interval; PCI: percutaneous coronary intervention; MI: myocardial infarction; TIMI: thrombolysis in myocardial infarction; REML: restricted maximum likelihood.

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Supplementary Appendix 3: Publication-bias and small-study effect assessment. S4. Funnel plot for post-PCI TIMI 3 flow in the broad pretreatment analysis. S5: Funnel plot for 30-day recurrent MI or reinfarction in the broad pretreatment analysis. S6: Funnel plot for 30-day stent thrombosis in the broad pretreatment analysis. S7: Funnel plot for 30-day all-cause mortality in the broad pretreatment analysis. S8: Funnel plot for in-hospital all-cause mortality in the broad pretreatment analysis. S9: Funnel plot for in-hospital/discharge major bleeding in the broad pretreatment analysis. CI: confidence interval; PCI: percutaneous coronary intervention; MI: myocardial infarction; TIMI: thrombolysis in myocardial infarction.

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Supplementary Table 1: Egger's and Begg's test assessment for publication bias

Outcome	Analysis	Egger's test p value	Begg's test p value	Interpretation
Post-PCI TIMI 3 flow	Broad main pretreatment analysis	0.612	1.000	No statistical evidence of small-study effects
30-day recurrent MI / reinfarction	Broad main pretreatment analysis	0.079	0.858	Egger test suggests possible small-study effects; Begg's test does not
30-day stent thrombosis	Broad main pretreatment analysis	0.110	0.049	Begg's test suggests possible small-study effects; Egger test does not
30-day all-cause mortality	Broad main pretreatment analysis	0.956	0.846	No statistical evidence of small-study effects
In-hospital all-cause mortality	Broad main pretreatment analysis	0.774	0.252	No statistical evidence of small-study effects
Major bleeding - in-hospital/discharge	Broad main pretreatment analysis	0.350	0.381	No statistical evidence of small-study effects
Strict prehospital outcomes	Strict sensitivity analysis	Not assessed	Not assessed	No strict-analysis outcome reached k≥10

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Supplementary Table 2: Knapp–Hartung sensitivity analyses for all outcome–time strata with fewer than 10 studies

Analysis	Outcome/time	k	Primary REML OR (95% CI)	Primary p value	Knapp–Hartung OR (95% CI)	KH p	Interpretation
Broad	Any bleeding - in-hospital/discharge	5	1.34 (0.85 to 2.11)	0.202	1.34 (0.78 to 2.30)	0.203	No statistically significant association in either analysis
Broad	Cardiogenic shock - in-hospital/discharge	3	0.67 (0.53 to 0.85)	<0.001	0.67 (0.42 to 1.07)	0.067	Primary significance not retained after Knapp–Hartung adjustment
Broad	MACE/MACCE - 1 year	3	1.05 (0.91 to 1.22)	0.510	1.05 (0.79 to 1.40)	0.536	No statistically significant association in either analysis
Broad	MACE/MACCE - 30 days	9	0.90 (0.73 to 1.10)	0.299	0.90 (0.72 to 1.12)	0.288	No statistically significant association in either analysis
Broad	MACE/MACCE - 6 months	3	0.89 (0.48 to 1.65)	0.704	0.89 (0.23 to 3.36)	0.736	No statistically significant association in either analysis
Broad	MACE/MACCE - in-hospital/discharge	4	0.94 (0.60 to 1.48)	0.799	0.94 (0.44 to 2.03)	0.824	No statistically significant association in either analysis
Broad	Major bleeding - 30 days	4	0.97 (0.85 to 1.12)	0.688	0.97 (0.83 to 1.14)	0.610	No statistically significant association in either analysis
Broad	All-cause mortality - 1 year	5	0.89 (0.71 to 1.11)	0.297	0.89 (0.66 to 1.21)	0.346	No statistically significant association in either analysis
Broad	All-cause mortality - 6 months	3	1.18 (1.09 to 1.29)	<0.001	1.18 (0.99 to 1.41)	0.054	Primary significance not retained after Knapp–Hartung adjustment
Broad	No-reflow - procedural	7	0.75 (0.53 to 1.06)	0.105	0.75 (0.51 to 1.09)	0.111	No statistically significant association in either analysis
Broad	Pre-PCI TIMI 2/3 flow - procedural	8	1.37 (1.03 to 1.83)	0.032	1.37 (0.96 to 1.95)	0.076	Primary significance not retained after Knapp–Hartung adjustment
Broad	Pre-PCI TIMI 3 flow - procedural	9	1.39 (1.03 to 1.88)	0.029	1.39 (0.96 to 2.01)	0.071	Primary significance not retained after Knapp–Hartung adjustment
Broad	Recurrent MI/reinfarction - 1 year	5	0.79 (0.70 to 0.89)	<0.001	0.79 (0.64 to 0.97)	0.034	Statistical significance retained
Broad	Recurrent MI/reinfarction - 6 months	3	0.77 (0.65 to 0.91)	0.002	0.77 (0.52 to 1.14)	0.102	Primary significance not retained after Knapp–Hartung adjustment
Broad	Recurrent MI/reinfarction - in-hospital/discharge	7	0.94 (0.39 to 2.26)	0.889	0.94 (0.30 to 2.97)	0.899	No statistically significant association in either analysis
Broad	Stent thrombosis - 6 months	3	0.53 (0.06 to 4.55)	0.563	0.53 (0.01 to 42.09)	0.596	No statistically significant association in either analysis
Broad	Stent thrombosis - in-hospital/discharge	5	1.03 (0.54 to 1.95)	0.932	1.03 (0.43 to 2.47)	0.934	No statistically significant association in either analysis
Broad	Stroke - 30 days	6	0.69 (0.56 to 0.85)	<0.001	0.69 (0.58 to 0.82)	0.003	Statistical significance retained
Broad	Stroke - in-hospital/discharge	6	0.93 (0.57 to 1.52)	0.764	0.93 (0.58 to 1.48)	0.693	No statistically significant association in either analysis
Direct prehospital	Major bleeding - in-hospital/discharge	4	0.94 (0.63 to 1.41)	0.770	0.94 (0.53 to 1.66)	0.757	No statistically significant association in either analysis
Direct prehospital	All-cause mortality - 30 days	4	0.98 (0.55 to 1.75)	0.958	0.98 (0.40 to 2.45)	0.961	No statistically significant association in either analysis
Direct prehospital	All-cause mortality - in-hospital/discharge	4	0.65 (0.27 to 1.56)	0.337	0.65 (0.20 to 2.18)	0.342	No statistically significant association in either analysis
Direct prehospital	Post-PCI TIMI 3 flow - procedural	3	1.17 (0.92 to 1.48)	0.197	1.17 (0.76 to 1.80)	0.263	No statistically significant association in either analysis
Direct prehospital	Pre-PCI TIMI 2/3 flow - procedural	4	1.71 (1.21 to 2.41)	0.002	1.71 (0.96 to 3.06)	0.061	Primary significance not retained after Knapp–Hartung adjustment

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Analysis	Outcome/time	k	Primary REML OR (95% CI)	Primary p value	Knapp–Hartung OR (95% CI)	KH p	Interpretation
Direct prehospital	Pre-PCI TIMI 3 flow - procedural	5	1.76 (1.08 to 2.89)	0.025	1.76 (0.88 to 3.54)	0.086	Primary significance not retained after Knapp–Hartung adjustment
Direct prehospital	Recurrent MI/reinfarction - 30 days	3	0.52 (0.31 to 0.87)	0.012	0.52 (0.24 to 1.13)	0.068	Primary significance not retained after Knapp–Hartung adjustment

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Supplementary Table 3: Leave-one-out sensitivity analysis for broad pretreatment outcome–time strata

Outcome/time	k	Primary OR (95% CI)	Primary p	Leave-one-out pooled OR range	Leave-one-out p range	Interpretation
Any bleeding - in-hospital/discharge	5	1.34 (0.85 to 2.11)	0.202	1.03 to 1.46	0.148 to 0.878	Null result retained in all leave-one-out analyses
Cardiogenic shock - in-hospital/discharge	3	0.67 (0.53 to 0.85)	<0.001	Not pooled after deletion (k=2)	-	Any single-study deletion left fewer than three studies; no pooled leave-one-out estimate was calculated
MACE/MACCE - 1 year	3	1.05 (0.91 to 1.22)	0.510	Not pooled after deletion (k=2)	-	Any single-study deletion left fewer than three studies; no pooled leave-one-out estimate was calculated
MACE/MACCE - 30 days	9	0.90 (0.73 to 1.10)	0.299	0.83 to 0.95	0.010 to 0.606	A statistically significant estimate emerged after omitting: Qadeer (2026)
MACE/MACCE - 6 months	3	0.89 (0.48 to 1.65)	0.704	Not pooled after deletion (k=2)	-	Any single-study deletion left fewer than three studies; no pooled leave-one-out estimate was calculated
MACE/MACCE - in-hospital/discharge	4	0.94 (0.60 to 1.48)	0.799	0.80 to 1.06	0.101 to 0.998	Null result retained in all leave-one-out analyses
Major bleeding - 30 days	4	0.97 (0.85 to 1.12)	0.688	0.84 to 1.00	0.320 to 0.952	Null result retained in all leave-one-out analyses
Major bleeding - in-hospital/discharge	14	1.05 (0.86 to 1.28)	0.655	0.95 to 1.11	0.369 to 0.870	Null result retained in all leave-one-out analyses
All-cause mortality - 1 year	5	0.89 (0.71 to 1.11)	0.297	0.83 to 0.97	0.147 to 0.786	Null result retained in all leave-one-out analyses
All-cause mortality - 30 days	15	0.91 (0.72 to 1.14)	0.397	0.86 to 0.96	0.208 to 0.717	Null result retained in all leave-one-out analyses
All-cause mortality - 6 months	3	1.18 (1.09 to 1.29)	<0.001	Not pooled after deletion (k=2)	-	Any single-study deletion left fewer than three studies; no pooled leave-one-out estimate was calculated
All-cause mortality - in-hospital/discharge	13	0.81 (0.59 to 1.10)	0.176	0.75 to 0.86	0.070 to 0.355	Null result retained in all leave-one-out analyses
No-reflow - procedural	7	0.75 (0.53 to 1.06)	0.105	0.63 to 0.81	0.006 to 0.287	A statistically significant estimate emerged after omitting: Yudi (2018)
Post-PCI TIMI 3 flow - procedural	10	1.09 (0.82 to 1.44)	0.569	1.02 to 1.19	0.040 to 0.867	A statistically significant estimate emerged after omitting: Gallo (2025)
Pre-PCI TIMI 2/3 flow - procedural	8	1.37 (1.03 to 1.83)	0.032	1.25 to 1.48	0.007 to 0.096	Primary significance lost after omitting: Fabris (2022), Pepe (2018), Postma (2014), Tohamy (2026)
Pre-PCI TIMI 3 flow - procedural	9	1.39 (1.03 to 1.88)	0.029	1.21 to 1.50	0.007 to 0.080	Primary significance lost after omitting: Fabris (2022), Lupi (2016), Tohamy (2026), Kovacevic (2025)
Recurrent MI/reinfarction - 1 year	5	0.79 (0.70 to 0.89)	<0.001	0.70 to 0.81	0.000 to 0.021	Primary significance retained in all leave-one-out analyses
Recurrent MI/reinfarction - 30 days	10	0.70 (0.50 to 0.96)	0.029	0.60 to 0.80	0.003 to 0.113	Primary significance lost after omitting: Larson (2010), Postma (2014)
Recurrent MI/reinfarction - 6 months	3	0.77 (0.65 to 0.91)	0.002	Not pooled after deletion (k=2)	-	Any single-study deletion left fewer than three studies; no pooled leave-one-out estimate was calculated
Recurrent MI/reinfarction - in-hospital/discharge	7	0.94 (0.39 to 2.26)	0.889	0.64 to 1.20	0.166 to 0.949	Null result retained in all leave-one-out analyses
Stent thrombosis - 30 days	10	0.65 (0.36 to 1.18)	0.156	0.56 to 0.73	0.009 to 0.305	A statistically significant estimate emerged after omitting: Qadeer (2026)
Stent thrombosis - 6 months	3	0.53 (0.06 to 4.55)	0.563	Not pooled after deletion (k=2)	-	Any single-study deletion left fewer than three studies; no pooled leave-one-out estimate was calculated
Stent thrombosis - in-hospital/discharge	5	1.03 (0.54 to 1.95)	0.932	0.78 to 1.31	0.422 to 0.955	Null result retained in all leave-one-out analyses
Stroke - 30 days	6	0.69 (0.56 to 0.85)	<0.001	0.67 to 0.84	0.000 to 0.558	Primary significance lost after omitting: Qadeer (2026)
Stroke - in-hospital/discharge	6	0.93 (0.57 to 1.52)	0.764	0.86 to 1.23	0.418 to 0.769	Null result retained in all leave-one-out analyses

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Supplementary Table 4: Targeted influence analyses for Qadeer (2026), Redfors (2019), and reconstructed Kovacevic (2025) data

Study omitted	Outcome/time	Primary k	Study random-effects weight %	Primary OR (95% CI); p	After exclusion
QADEER2026	MACE/MACCE - 1 year	3	57.5	1.05 (0.91 to 1.22); p=0.510	Not pooled after exclusion (k=2)
QADEER2026	MACE/MACCE - 30 days	9	16.8	0.90 (0.73 to 1.10); p=0.299	0.83 (0.72 to 0.96); p=0.010
QADEER2026	MACE/MACCE - 6 months	3	45.9	0.89 (0.48 to 1.65); p=0.704	Not pooled after exclusion (k=2)
QADEER2026	Major bleeding - 30 days	4	83.7	0.97 (0.85 to 1.12); p=0.688	0.84 (0.59 to 1.19); p=0.320
QADEER2026	All-cause mortality - 1 year	5	27.7	0.89 (0.71 to 1.11); p=0.297	0.83 (0.65 to 1.07); p=0.147
QADEER2026	All-cause mortality - 30 days	15	11.3	0.91 (0.72 to 1.14); p=0.397	0.88 (0.69 to 1.13); p=0.325
QADEER2026	All-cause mortality - 6 months	3	99.6	1.18 (1.09 to 1.29); p=0.000	Not pooled after exclusion (k=2)
QADEER2026	Recurrent MI/reinfarction - 1 year	5	39.8	0.79 (0.70 to 0.89); p=0.000	0.70 (0.56 to 0.88); p=0.003
QADEER2026	Recurrent MI/reinfarction - 30 days	10	28.8	0.70 (0.50 to 0.96); p=0.029	0.60 (0.43 to 0.84); p=0.003
QADEER2026	Recurrent MI/reinfarction - 6 months	3	97.8	0.77 (0.65 to 0.91); p=0.002	Not pooled after exclusion (k=2)
QADEER2026	Stent thrombosis - 30 days	10	14.8	0.65 (0.36 to 1.18); p=0.156	0.56 (0.36 to 0.86); p=0.009
QADEER2026	Stent thrombosis - 6 months	3	50.0	0.53 (0.06 to 4.55); p=0.563	Not pooled after exclusion (k=2)
QADEER2026	Stroke - 30 days	6	86.3	0.69 (0.56 to 0.85); p=0.001	0.84 (0.47 to 1.50); p=0.558
REDFORS2019	All-cause mortality - 30 days	15	11.3	0.91 (0.72 to 1.14); p=0.397	0.94 (0.74 to 1.20); p=0.635
REDFORS2019	Stent thrombosis - 30 days	10	15.7	0.65 (0.36 to 1.18); p=0.156	0.60 (0.30 to 1.19); p=0.140
KOVACEVIC2025	All-cause mortality - 30 days	15	9.3	0.91 (0.72 to 1.14); p=0.397	0.86 (0.69 to 1.09); p=0.208
KOVACEVIC2025	All-cause mortality - in-hospital/discharge	13	10.9	0.81 (0.59 to 1.10); p=0.176	0.75 (0.55 to 1.02); p=0.070
KOVACEVIC2025	Pre-PCI TIMI 3 flow - procedural	9	12.9	1.39 (1.03 to 1.88); p=0.029	1.38 (0.98 to 1.94); p=0.069

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Supplementary Table 5: Post hoc exploratory timing-definition analysis for highly heterogeneous pre-PCI TIMI outcomes

Outcome	Timing subgroup	k	OR (95% CI)	p for effect	p for interaction
Pre-PCI TIMI 2/3 flow	Direct prehospital	4	1.71 (1.21 to 2.41)	0.002	0.071
Pre-PCI TIMI 2/3 flow	Other early/upstream	4	1.09 (0.77 to 1.55)	0.627	
Pre-PCI TIMI 3 flow	Direct prehospital	5	1.76 (1.08 to 2.89)	0.025	0.155
Pre-PCI TIMI 3 flow	Other early/upstream	4	1.12 (0.82 to 1.53)	0.467	

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