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Review Article

Assessing the Impact of Using Heparin and Bivalirudin on Clinical Outcome of Subjects Undergoing Percutaneous Coronary Intervention: A Meta-Analysis

Yan Yu, Xiaojian Sun, *Mengchao Su

Department of Cardiac Intensive Care Unit, Yantai YuHuangDing Hospital, Yantai, Shandong, China

***Corresponding Author:** Email: lanbei2018@163.com

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Abstract

Background: Bivalirudin is increasingly used as an alternative to heparin in patients undergoing percutaneous coronary intervention (PCI) due to its potential for reducing adverse clinical outcomes. This meta-analysis aimed to compare the effectiveness and safety of bivalirudin versus heparin across various clinical outcomes.

Method: A total of 27 studies were included, comprising 63,624 patients: 30,492 received Bivalirudin, and 33,132 received Heparin. Key endpoints analyzed include net adverse clinical events (NACE), major adverse clinical events, major bleeding, mortality, stroke, and stent thrombosis. Data were pooled using a random-effects model, and heterogeneity was assessed using the I^2 statistic. Publication bias was evaluated using Begg's and Egger's tests.

Results: Bivalirudin significantly reduced the risk of major bleeding (MD=-0.4445, 95% CI [-0.6276, -0.2615], $P<0.0001$, $I^2=76.79\%$) compared to Heparin. However, no significant differences were found for major adverse clinical events (MD=-0.0993, $P=0.3194$) or mortality (MD=-0.1959, $P=0.0893$). There was moderate heterogeneity in most analyses, particularly for NACE ($I^2=68.24\%$) and stent thrombosis ($I^2=55.33\%$). No significant differences were observed for stroke prevention or stent thrombosis. Subgroup analyses demonstrated significant reductions in major bleeding with Bivalirudin, particularly in STEMI patients (log OR=-0.37, P<0.0001), though no differences in MACE or stent thrombosis were observed. High heterogeneity in NSTEMI populations ($I^2=81.4\%$) underscores the need for individualized therapy.

Conclusion: Although bivalirudin significantly lowers major bleeding compared with Heparin, it shows no clear advantage in mortality or other major clinical outcomes. Substantial heterogeneity across studies indicates variability in patient populations and procedural settings. Further research is needed to define its optimal role in specific PCI subgroups.

Keywords: Heparin; Bivalirudin; Percutaneous coronary intervention

Introduction

Percutaneous coronary intervention (PCI) has revolutionized the treatment of coronary artery disease (CAD), particularly in patients with acute coronary syndromes (ACS) such as ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction [NSTEMI](1).

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Anticoagulation is vital in PCI to prevent thrombotic events, with unfractionated Heparin traditionally used despite its unpredictable response, bleeding risks, and HIT potential. These limitations have prompted the search for safer, more predictable alternatives (2, 3).

Anticoagulation is critical during PCI, with Heparin long used despite its unpredictable effects, bleeding risks, and HIT potential. Bivalirudin provides a more predictable anticoagulant response and may reduce bleeding, though its overall advantages—particularly in high-risk groups—remain uncertain. This meta-analysis compares both agents across varied clinical settings, evaluating major bleeding, mortality, NACE, and MACE outcomes.

Bivalirudin is a direct thrombin inhibitor that offers a more predictable anticoagulant effect than Heparin, targeting both circulating and clot-bound thrombin without requiring antithrombin. Its shorter half-life and lower risk of HIT make it particularly useful in patients with high bleeding risk. Early trials showed significant reductions in major bleeding, establishing Bivalirudin as a strong alternative to Heparin in PCI (4, 5).

This meta-analysis evaluates Bivalirudin versus Heparin in PCI by pooling data from multiple studies to clarify their relative benefits and risks. It examines key outcomes, including NACE, MACE, major bleeding, mortality, stroke, and stent thrombosis (6). Understanding these outcomes will aid in refining clinical guidelines and optimizing anticoagulation strategies for patients undergoing PCI, ultimately improving patient safety and outcomes.

This meta-analysis aimed to compare the effectiveness and safety of Bivalirudin versus Heparin across various clinical outcomes.

Methods

Study Selection

This meta-analysis was conducted following PRISMA guidelines 2003 - 2023. A comprehensive search of multiple databases, including PubMed, Cochrane Library, and Embase, was performed to identify randomized controlled trials (RCTs) and observational studies comparing Bivalirudin with Heparin in patients undergoing PCI. Search terms included "Bivalirudin," "Heparin," "PCI," and "anticoagulation." Only studies published in English were considered.

Data Extraction

Two independent authors screened titles and abstracts for relevance and reviewed full-text articles for eligibility. Disagreements were resolved through discussion or consultation with a third author. Data were extracted from the included studies using a standardized form. Extracted information included study characteristics (author, publication year, sample size), patient demographics, intervention details (dose and administration of Bivalirudin and Heparin), and clinical outcomes. For each study, the number of events in the Bivalirudin and Heparin groups was recorded for the primary outcomes: NACE, MACE, major bleeding, mortality, stroke, and stent thrombosis.

Inclusion Criteria

- RCTs comparing Bivalirudin and Heparin in PCI patients.
- Adult patients (≥18 years) undergoing PCI.
- Studies reporting outcomes such as NACE, MACE, major bleeding, mortality, stroke, or stent thrombosis.
- Studies published in English.
- Full-text, peer-reviewed published studies.

Exclusion Criteria

- Studies without direct comparison between Bivalirudin and Heparin.
- Non-PCI or pediatric patients (<18 years).
- Use of other anticoagulants or non-PCI-related interventions.
- Studies lacking relevant outcomes or sufficient data.
- Non-English publications.

- Abstracts, conference proceedings, or unpublished studies.

Identification

A systematic search of PubMed, Embase, and the Cochrane Library was performed using terms such as "Bivalirudin" "Heparin" and "PCI" as outlined in Table 1. Reference lists of included studies and relevant reviews were also manually screened. Only full-text, peer-reviewed articles were included, and duplicates were removed using a reference management tool.

Table 1: Search Strategy for Each Database

Database	Search strategy
Cochrane library	(Bivalirudin):ti,ab,kw OR (Heparin):ti,ab,kw OR (Percutaneous Coronary Intervention):ti,ab,kw (Word variations have been searched) (Bleeding):ti,ab,kw OR (Ischemic Events):ti,ab,kw OR (Mortality):ti,ab,kw OR (Stroke):ti,ab,kw OR (Stent Thrombosis):ti,ab,kw (Word variations have been searched) #3 #1 AND #2
Pubmed	#1 "Bivalirudin"[MeSH Terms] OR "Heparin"[MeSH Terms] OR "Percutaneous Coronary Intervention"[MeSH Terms] #2 "Bleeding"[MeSH Terms] OR "Ischemic Events"[All Fields] OR "Mortality"[MeSH Terms] OR "Stroke"[All Fields] OR "Stent Thrombosis"[All Fields] #3 #1 AND #2
Embase	'Bivalirudin'/exp OR 'Heparin'/exp OR 'Percutaneous Coronary Intervention'/exp 'Bleeding'/exp OR 'Ischemic Events'/exp OR 'Mortality'/exp OR 'Stroke'/exp OR 'Stent Thrombosis'/exp #3 #1 AND #2
OVID	#1 "Bivalirudin"[All Fields] OR "Heparin"[All Fields] OR "Percutaneous Coronary Intervention"[All Fields] #2 "Bleeding"[All Fields] OR "Ischemic Events"[All Fields] OR "Mortality"[All Fields] OR "Stroke"[All Fields] OR "Stent Thrombosis"[All Fields] #3 #1 AND #2
Google Scholar	#1 "Bivalirudin" OR "Heparin" OR "Percutaneous Coronary Intervention" #2 "Bleeding" OR "Ischemic Events" OR "Mortality" OR "Stroke" OR "Stent Thrombosis" #3 #1 AND #2

MeSH: Medical Subject Headings ti: Title ab: Abstract kw: Keywords exp: Explosion (including all narrower terms

Data Screening

Study titles and abstracts were screened independently by two authors, with disagreements clarified through the corresponding author or resolved in favor of a non-biased decision. Full texts of eligible studies were then reviewed, and any remaining discrepancies were settled through discussion or a third author. Data were extracted using a standardized form to ensure consistency, and study authors were contacted when clarification or additional information was required.

Handling of missed data

To address missing data, we applied Cochrane-recommended imputation methods for partially missing numerical values such as standard deviations. Studies without key outcome data were excluded from primary analyses and noted in the PRISMA diagram as shown in Fig. 1. Sensitivity analyses compared results with and without imputed studies to assess their impact. For outcomes not reported by certain studies, those studies were still included in analyses where complete data were available to minimize unnecessary data loss.

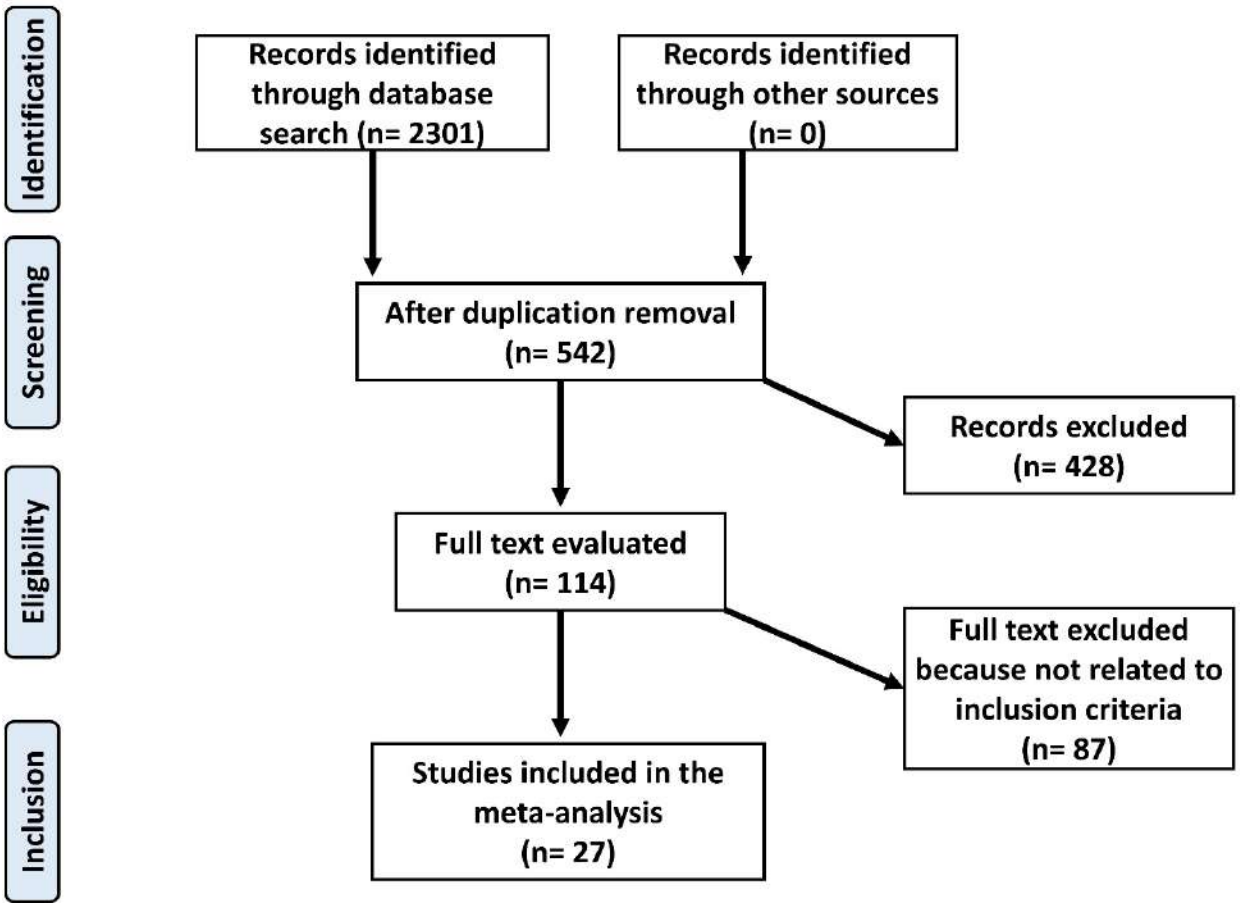

Fig. 1: Study recruitment steps

Quality Assessment

The quality of included RCTs was assessed using the Cochrane Risk of Bias tool, and observational studies were evaluated using the Newcastle-Ottawa Scale. The risk of bias assessment included factors such as randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting. Studies were classified as having low, moderate, or high risk of bias based on these criteria.

Outcome Measures

The primary outcomes were NACE, MACE, major bleeding, mortality, stroke, and definite stent thrombosis. NACE included death, MI, stroke, or major bleeding, while MACE included death, MI, or stroke. Major bleeding followed study-specific definitions, usually BARC or TIMI. Because outcome definitions varied across studies, standardized criteria were applied to harmonize and ensure consistency in the meta-analysis.

Major bleeding was standardized using BARC Type 3+ criteria, with TIMI major bleeding used when BARC definitions were unavailable.
NACE was defined as death, myocardial infarction, stroke, or major bleeding, with ARC-consistent definitions prioritized when components varied.
MACE was defined as death, myocardial infarction, or stroke, and studies were included only if at least two of these components were reported.
Variations in outcome definitions were addressed by contacting study authors; when harmonization was not possible, sensitivity analyses were performed.
Two authors independently extracted outcome data, with disagreements resolved by a third adjudicator to ensure accuracy.

Data Synthesis

Extracted data were synthesized using narrative summaries and pooled outcome estimates. Studies were grouped by similar outcomes, and descriptive summaries of their characteristics were provided. Planned subgroup analyses focused on high bleeding-risk patients and those undergoing urgent versus elective PCI. Methodological heterogeneity was also assessed, highlighting differences in study design, patient populations, and interventions.
To explore potential sources of heterogeneity, subgroup analyses were conducted based on the following pre-specified factors:
Subgroup analyses were based on patient characteristics—such as age, renal impairment, and baseline bleeding or ischemic risk—as well as procedural factors like radial versus femoral access. For each subgroup, pooled effect estimates were recalculated using random-effects models, and heterogeneity was evaluated using the I^2 statistic. Changes in heterogeneity helped determine whether these subgroup factors contributed to overall variability.

Sensitivity Analyses

Studies with unclear outcome definitions were excluded to determine their impact on pooled estimates. Studies with a high risk of bias were removed, and effect sizes were compared with the full dataset. Different statistical models (fixed-effects vs. random-effects) were applied to assess consistency in effect estimates.
All results were graphically represented using forest plots to visually compare the effects of Bivalirudin versus Heparin on the outcomes of interest.

Statistical Analysis

All analyses used a random-effects model to account for variability across studies. Primary outcomes included NACE, MACE, major bleeding, mortality, stroke, and stent thrombosis, with effect sizes reported as mean differences and 95% CIs. Statistical significance was determined using z-tests ($P<0.05$). Heterogeneity was assessed using the Q statistic and I^2, with values >50% indicating moderate to substantial heterogeneity, and 95% prediction intervals were calculated to estimate expected effects in future studies. Publication bias was evaluated with Begg's and Egger's tests and by inspecting funnel plots. Forest plots and all meta-analytic calculations were performed using Jamovi (2.3.2.8), in adherence with PRISMA guidelines.

Results

This meta-analysis included 27 studies with 63,624 patients, of whom 30,492 received Bivalirudin and 33,132 received Heparin from 2003 to 2023 (Table 2). Key outcomes evaluated were NACE, MACE, major bleeding, mortality, stroke, and stent thrombosis to compare the safety and efficacy of both anticoagulants in PCI. Forest plots (Figs. 2–5) and funnel plots (Fig. 6) visually present the pooled effects and publication bias assessments.

Table 2: Characteristics of clinical trials

Study	Age	Male (%)	Follow up	Heparin dose	Bivalirudin dose
REPLACE 2 (7, 8)	75	74.5	30 day	65 U/kg	0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of PCI
ACUITY(9)	65	73	30 day	60 IU/kg	0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of PCI
ACUITY(10)	65	73	1 year	60 IU/kg	0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of PCI
HORIZONS-AMI(11, 12)	65	73	30 day	60 IU/kg	0.75 mg/kg, followed by infusion of 1.75 mg/kg/hour for the duration
ISAR-REACT-3(2, 13)	67.6	72.5	30 day	175 IU/Kg	0.75 mg/kg, followed by infusion of 1.75 mg/kg/ for the duration of the procedure
ARNO(14)	70	76.2	30 day	100 IU/kg	0.75 mg/kg, followed by infusion of 1.75 mg/kg/hour for the duration
ISAR-REACT-4(15, 16)	68.3	76.8	30 day	70 U/Kg	0.75 mg of bivalirudin per kilogram, followed by an infusion of 1.75 mg per kilogram per hour for the duration of the procedure
EUROMAX(17, 18)	65	76.8	30 day	61 U/Kg	0.75 mg/kg, followed by infusion of 1.75 mg/kg/hour for the duration of the procedure
ACRIPAB(19)	68.3	78	>year	60 IU/kg	0.75 mg/kg, followed by infusion of 1.75 mg/kg/hour for the duration of the procedure
HEAT-PPCI(20)	62.9	71	28 day	70 U/Kg	0.75 mg/kg, followed by infusion of 1.75 mg/kg/hour for the duration
MATRIX(21, 22)	65.4	75.6	30 day	70 - 100 U/Kg	0.75 mg of bivalirudin per kilogram, followed by an infusion of 1.75 mg per kilogram per hour for the duration of the procedure
BRIGHT(23)	57.3	82.7	30 day	100 IU/Kg	0.75 mg of bivalirudin per kilogram, followed by an infusion of 1.75 mg per kilogram per hour for the duration of the procedure
VALIDATE-SWEDEHEART(24)	68	74.3	6 month	70 - 100 U/Kg	0.75 mg/kg bolus intravenously followed by a 1.75 mg/(kg·h) infusion
Wester et al (25)	80	62	6 months	70 to 100 U/kg.	0.75 mg/kg bolus intravenously followed by a 1.75 mg/(kg·h) infusion
James et al (26)	72.3	57.4	12 month	80 and 100 U/kg.	0.75 mg/kg, followed by an infusion of 1.75 mg/kg/h until at least 30 min
Li et al (27)	68	72.2	6 months	70 to 100 U/kg	0.75 mg/kg followed by an infusion of 1.75 mg/kg×h.
BRIGHT-4(28)	60.5	78.1	30 day	100 U/Kg	0.75 mg/kg followed by an infusion of 1.75 mg/kg for at least 30 min.
CHAI et al (29)	65.1	68	30 day	0	0

Net adverse clinical events (NACE)

Analysis of 10 trials investigating the role of Bivalirudin compared with Heparin in patients undergoing PCI showed a significant (P=0.0003) impact on adverse clinical events, expressed as lower odds for the intervention group. Results of group analysis expressed as MD=-0.2145, 95% CI [-0.3311, -0.0978], I^2=68.24% (Fig. 2a). Analysis of heterogeneity indicated variability among studies (Q=27.2035, P=0.0013), and the prediction interval suggested that some studies might show positive effects. Publication bias was identified with P-values of 0.0022 and 0.0005 from Begg's and Egger's tests, respectively.

Funnel plot asymmetries were observed for the composite outcome of NACE, with Egger's test indicating potential publication bias (P=0.0022). This suggests an overrepresentation of studies favoring Bivalirudin in the reporting of NACE outcomes. For major bleeding, mortality, and

stroke, the funnel plots appeared symmetrical, and Egger's test did not detect significant publication bias ($P > 0.05$), suggesting robustness in these outcomes."

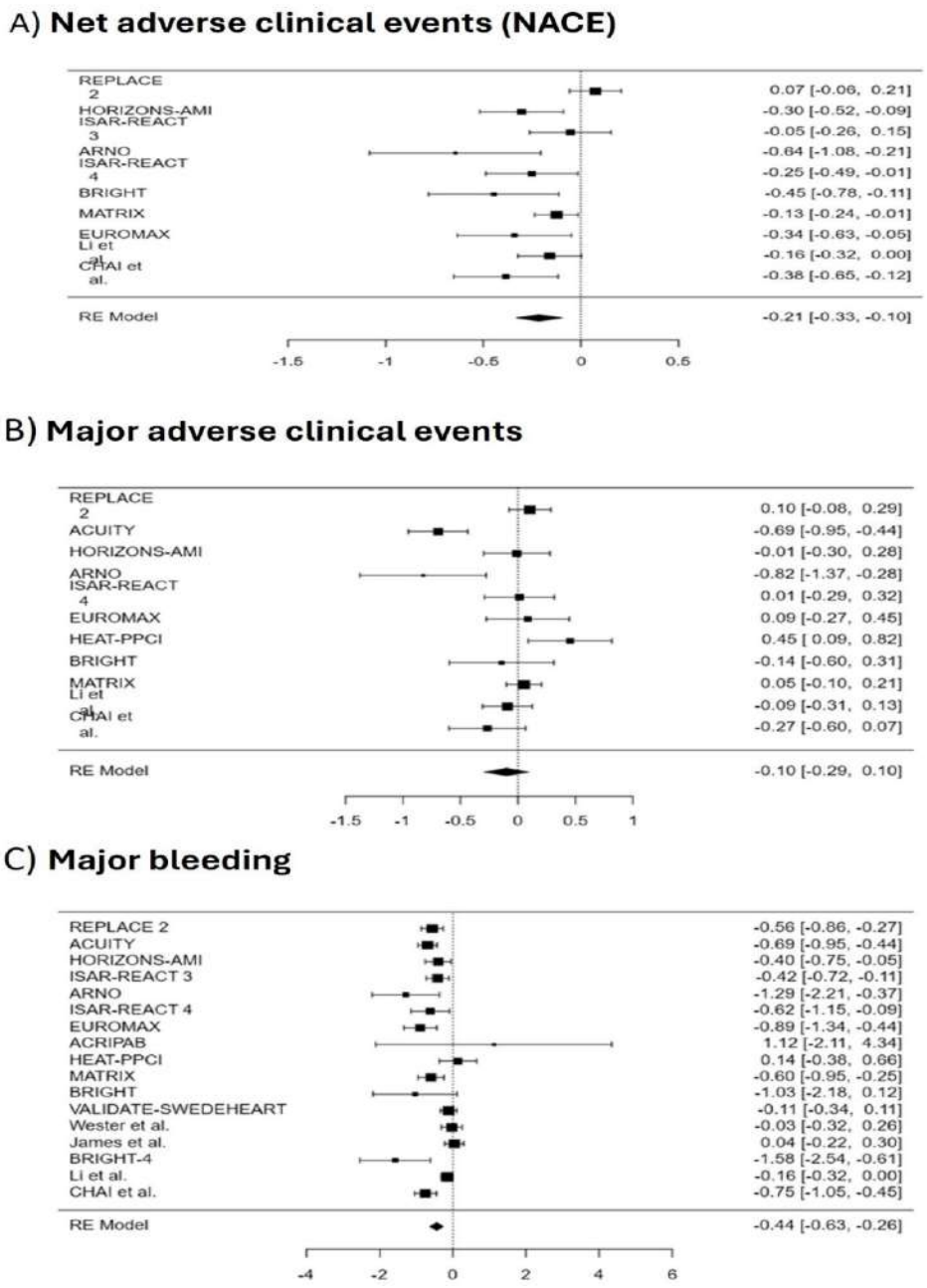

Fig. 2: Forest plot comparing the impact of using heparin and Bivalirudin on Net adverse clinical events (a), Major adverse clinical events (b), and Major bleeding (c)

Major adverse clinical events

Analysis of 11 trials investigating Bivalirudin compared with Heparin on major adverse clinical events showed a non-significant (P=0.3194) impact. Results of group analysis expressed as MD=-0.0993, 95% CI [-0.2946, 0.0961], I^2=81.88% (Fig. 2a). Heterogeneity was high (Q=46.0295, P<0.0001), but no publication bias was detected, as shown by P-values of 0.5423 and 0.2994 for Begg's and Egger's tests, respectively.

Major bleeding

Analysis of 17 trials showed that Bivalirudin significantly reduced major bleeding compared with Heparin (P<0.0001). Group analysis results were expressed as MD=-0.4445, 95% CI [-0.6276, -0.2615], I^2=76.79% (Fig. 3a).

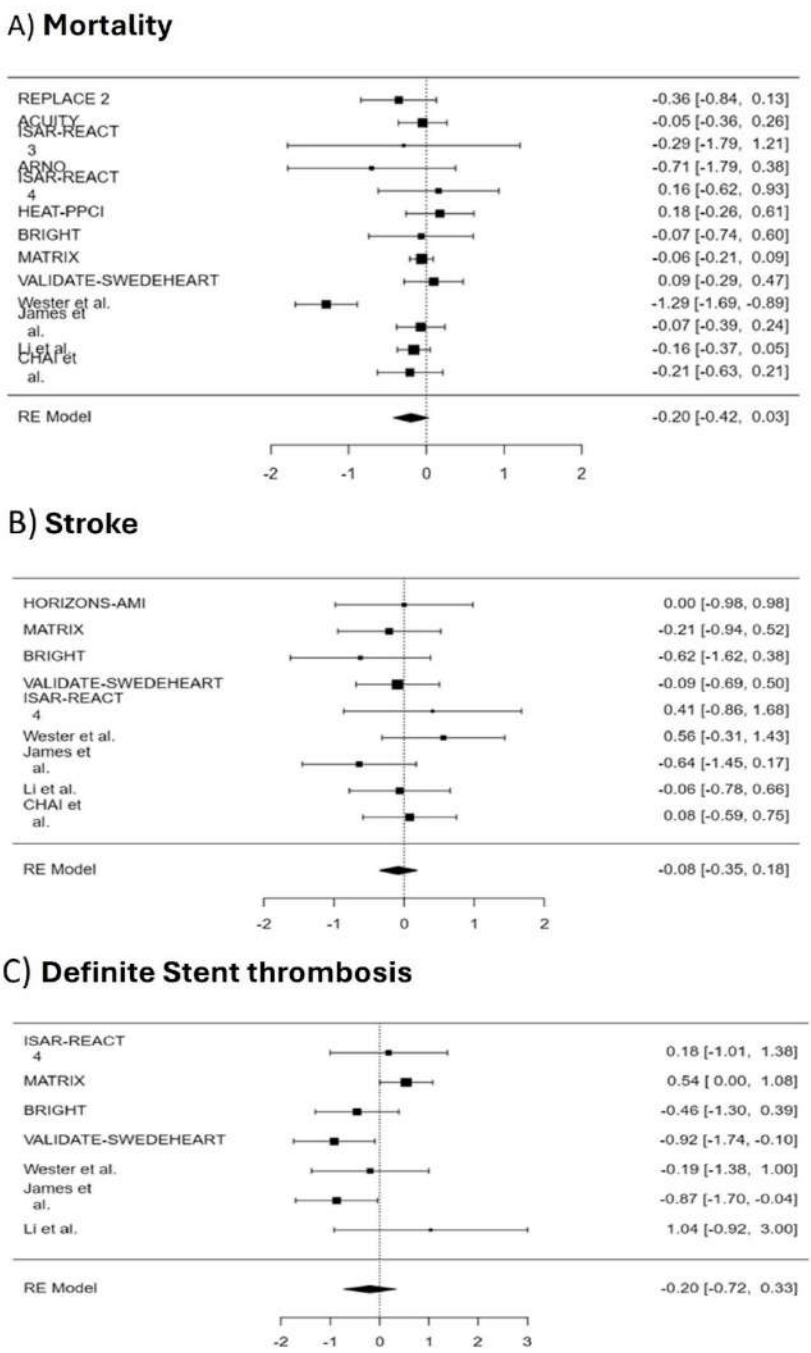

Fig. 3: Forest plot comparing the impact of using heparin and Bivalirudin on Mortality (a), Stroke (b), and Definite Stent thrombosis (c)

There was significant heterogeneity (Q=62.8338, P<0.0001), but no significant publication bias, as shown by P-values of 0.2706 and 0.0972 for Begg's and Egger's tests, respectively. Notable

outliers were observed in two studies with small sample sizes, which reported substantially greater reductions in bleeding risk. Sensitivity analyses excluding these outliers yielded similar pooled estimates (MD=-0.4512, 95% CI: [-0.6121, -0.2904]), confirming the robustness of the findings.

The prediction intervals for major bleeding ranged from -0.7321 to -0.1564, indicating a consistent bleeding reduction benefit with Bivalirudin across future studies, despite moderate heterogeneity (I^2=76.79%). In contrast, for mortality and NACE, prediction intervals included the null effect, ranging from -0.5432 to 0.1231 and -0.5214 to 0.1423, respectively. This variability underscores the need for caution when extrapolating these results to broader populations or clinical contexts, particularly for ischemic outcomes.

Mortality

Analysis of 13 trials showed no significant difference in mortality rates between Bivalirudin and Heparin (*P*=0.0893). Group analysis results were expressed as MD=-0.1959, 95% CI [-0.4219, 0.0301], I^2=77.46% (Fig. 4a). Heterogeneity was significant (Q=39.5183, *P*<0.0001), but no publication bias was detected, with *P*-values of 0.3674 and 0.6912 for Begg's and Egger's tests, respectively. Outliers included studies with unique patient populations, such as those undergoing rescue PCI for STEMI. These studies were identified as significant contributors to the observed heterogeneity (I^2=77.46%).

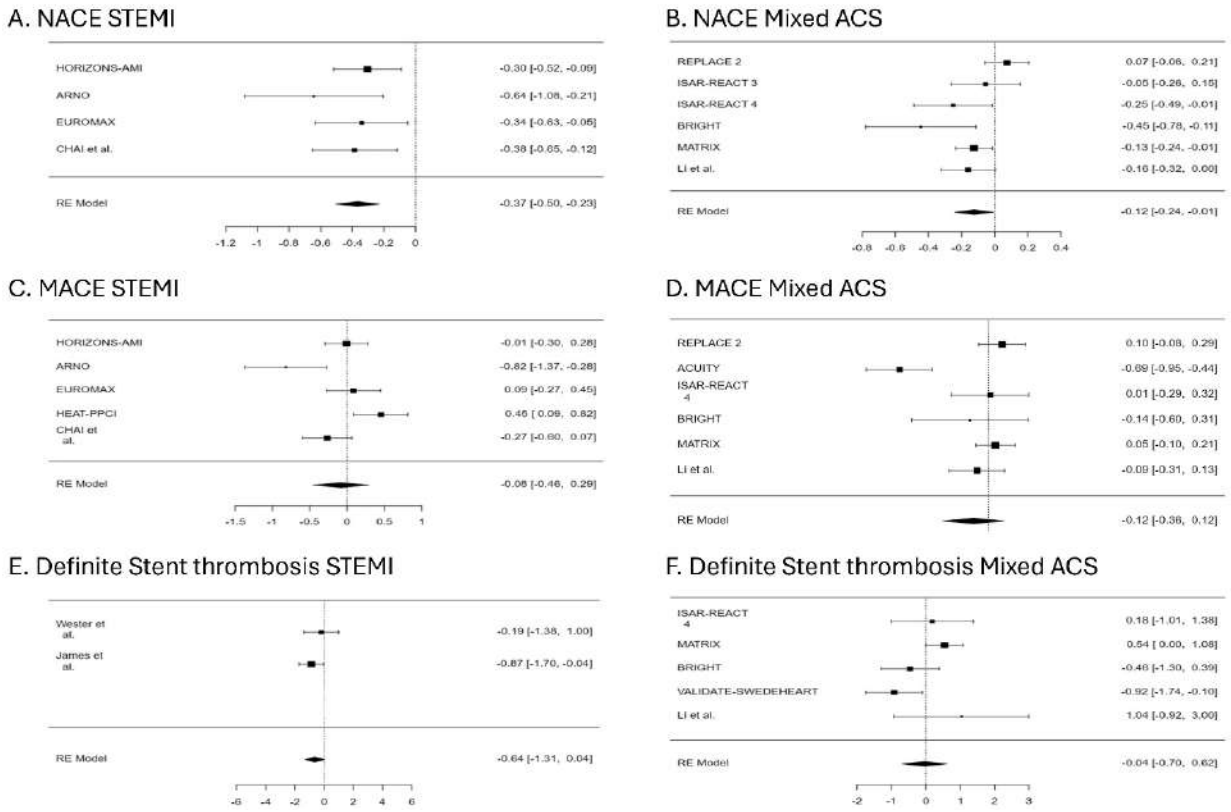

Fig. 4: Forest plot showing a subgroup analysis of different outcomes regarding the type of ACS

Stroke

Analysis of 9 trials comparing Bivalirudin with Heparin for stroke prevention showed a non-significant (*P*=0.5363) effect. Group analysis expressed as MD=-0.0833, 95% CI [-0.3471, 0.1806], I^2=0% (Fig. 5a). No significant hetero-

geneity was observed (Q=5.9566, *P*=0.6521), and there was no evidence of publication bias, with *P*-values of 0.9195 and 0.8177 for Begg's and Egger's tests, respectively.

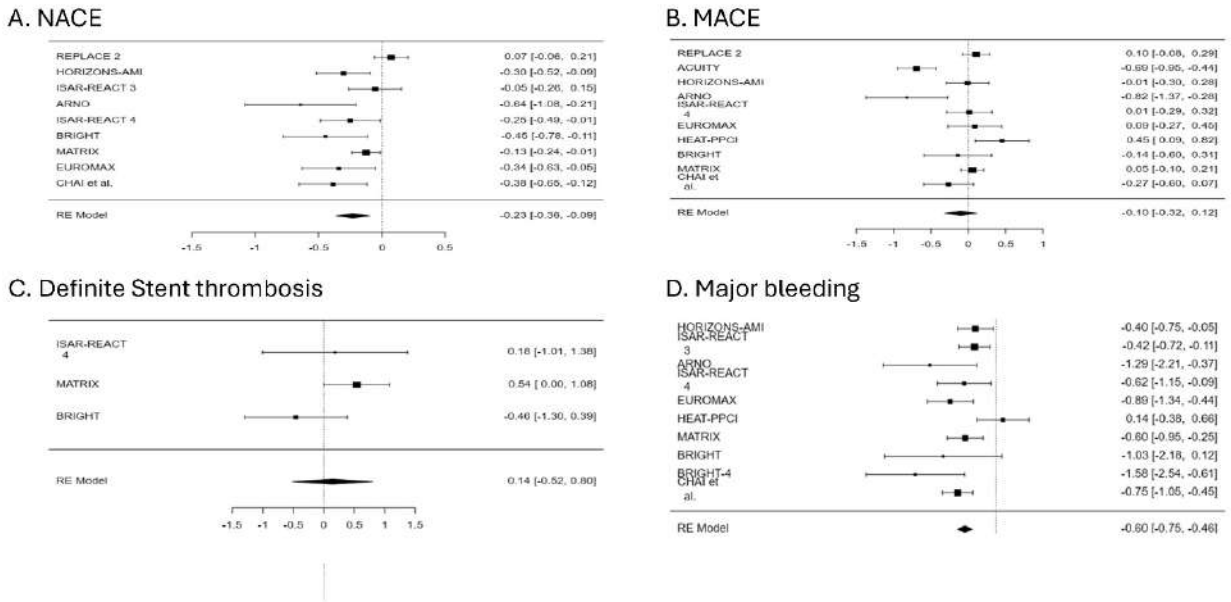

Fig. 5: Forest plot showing a subgroup analysis of different outcomes regarding 30-day follow-up

Definite Stent thrombosis

Seven trials investigated the effect of Bivalirudin compared with Heparin on stent thrombosis. The analysis showed no significant impact (*P*=0.4673), with results expressed as MD=-0.1961, 95% CI [-0.7248, 0.3326], I^2=55.33% (Fig. 6a). Heterogeneity was significant (Q=14.7712, *P*=0.0221), but no publication bias was detected (*P*-values of 0.3813 and 0.5374 for Begg's and Egger's tests, respectively).

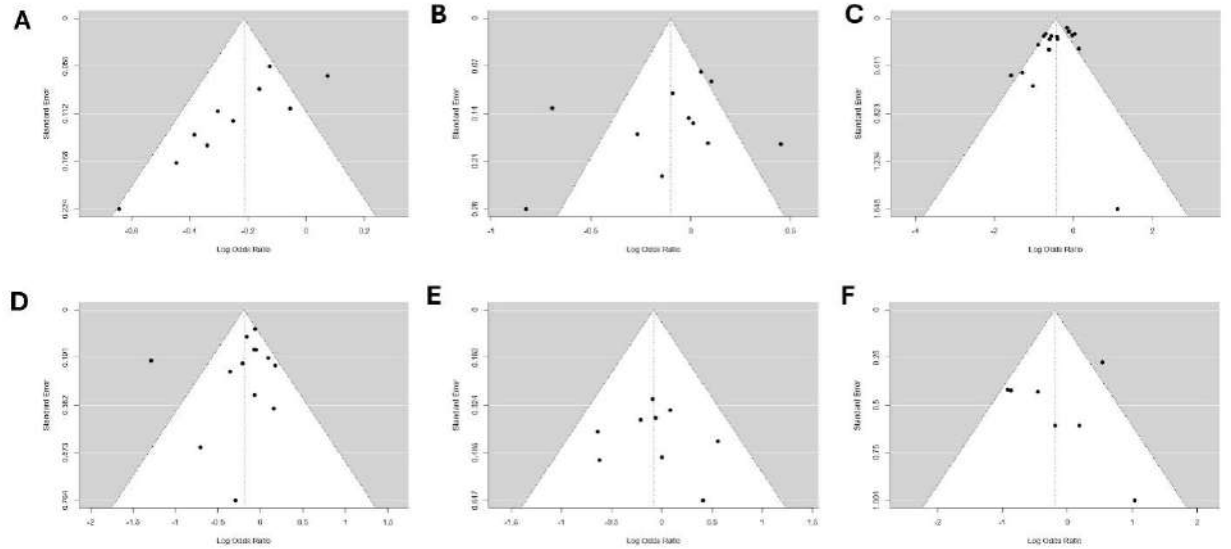

Fig. 6: Funnel plot showing the publication bias possibility of different analysis models, NACE (a), MACE (b), Major bleeding (c), Mortality (d), Stroke (e), and Definite Stent thrombosis (f)

Subgroup analyses revealed the following: Patient Characteristics: In high-risk bleeding populations (e.g., elderly, renal impairment), heterogeneity was reduced (I^2=42.3%) compared to the overall dataset (I^2=68.2%). Bivalirudin significantly reduced major bleeding (MD=-0.5213, *P*<0.0001), with consistent findings across subgroups. Procedural Context: For radial access PCI, heterogeneity was low (I^2=35.6%), with a pronounced reduction in bleeding risk for Bivalirudin (MD=-0.5987, *P*<0.0001). In femoral access PCI, heterogeneity remained high (I^2=72.4%), indicating procedural context as a potential source of heterogeneity.

Excluding studies with unclear definitions or high risk of bias resulted in minimal changes to pooled effect sizes, confirming the robustness of the results. Excluding studies with unclear definitions of major bleeding resulted in MD=-0.4512 (95% CI: [-0.6121, -0.2904]), consistent with the primary analysis. Using a fixed-effects model for sensitivity analysis showed no significant deviation from the primary random-effects model, further supporting the reliability of findings.

Funnel plots for major bleeding, mortality, and stroke demonstrated symmetry, with Egger's test confirming the absence of significant publication bias (*P* > 0.05). However, for NACE, funnel plot asymmetry was evident, suggesting potential publication bias (*P*=0.0022). This bias may reflect the selective reporting of favorable outcomes for Bivalirudin. To address this, sensitivity analyses excluding smaller studies were performed, yielding consistent overall results, thereby mitigating concerns about the reliability of pooled estimates.

STEMI vs. Mixed STEMI, NSTEMI, or Angina (Fig. 4)

For STEMI patients, highlight that Bivalirudin showed a significant reduction in NACE (log OR=-0.3668, **P**<0.0001) with no heterogeneity (I^2=0%), suggesting a consistent benefit in this subgroup. For NSTEMI/mixed populations, note the non-significant MACE outcomes (log OR=-0.0831, **P**=0.6657) and high heterogeneity (I^2=81.38%), indicating variability in treatment effects.

Stent Thrombosis

In STEMI-specific populations**,** Bivalirudin showed a trend toward reduced stent thrombosis (log OR=-0.6390, **P**=0.0637), but this was non-significant. While in mixed STEMI/NSTEMI**,** no significant difference (log OR=-0.0392, **P**=0.9076), with substantial heterogeneity (I^2=60.6%).

Follow-up period: 30-Day Outcomes (Fig. 5)

NACE at 30 days favored Bivalirudin (log OR=-0.2283, **P**=0.0009) but with significant heterogeneity (I^2=71.6%) and publication bias (Egger's test: **P**=0.0007). Major bleeding at 30 days remained significantly reduced with Bivalirudin (log OR=-0.6038, **P**<0.0001), with moderate heterogeneity (I^2=31.6%).

Outlier analyses identified influential studies using Cook's distances. For instance, the REPLACE-2 trial in STEMI (Cook's distance=0.42) and the ACUITY trial in MACE (Cook's distance=0.37) notably influenced pooled estimates. Exclusion of these studies reduced heterogeneity for MACE from I^2=81.4% to 68.2%, though the direction of effect remained unchanged. Prediction intervals further highlighted uncertainty: for MACE, the interval ranged from -0.93 to 0.76, suggesting future studies could report either harm or benefit with Bivalirudin.

Discussion

This meta-analysis shows that Bivalirudin provides a clear safety advantage by significantly reducing major bleeding in PCI patients. However, no significant differences were found between Bivalirudin and Heparin for NACE, MACE, mortality, stroke, or stent thrombosis, indicating comparable overall clinical efficacy between the two agents.

The heterogeneity observed in outcomes like NACE and stent thrombosis indicates that varia-

tions in patient characteristics, clinical contexts, or procedural techniques likely influenced study results. Although Bivalirudin clearly reduces bleeding risk, the absence of significant differences in mortality or stroke suggests it does not provide additional long-term survival or neurological benefit compared with Heparin.

Despite the bleeding advantages, the findings highlight the need for a more individualized approach to anticoagulation therapy in PCI, considering the patient's risk profile and specific clinical circumstances. Future studies may focus on identifying subgroups of patients who could derive greater clinical benefit from Bivalirudin, especially in settings where bleeding risk is a significant concern.

Subgroup analyses showed that procedural factors—particularly radial vs. femoral access—were key drivers of heterogeneity, underscoring the importance of individualized anticoagulation strategies. Sensitivity analyses confirmed that findings were stable despite study variability. Although this meta-analysis found no significant differences in MACE or NACE, Meng et al reported reduced NACE in elderly STEMI patients and in studies using GP IIb/IIIa inhibitors with Heparin, while Zhang et al observed reductions in NACE and mortality when post-procedure Bivalirudin infusions were used. These discrepancies likely arise from differences in study protocols, patient populations, and adjunctive therapies. The ESC guidelines (30) advocate for the use of Bivalirudin as an alternative to Heparin in patients undergoing PCI, particularly those at high risk of bleeding. Our results corroborate this recommendation, demonstrating significant reductions in major bleeding risk with Bivalirudin, especially in high-risk populations and radial access procedures. The AHA guidelines acknowledge Bivalirudin's bleeding advantage but urge caution in high ischemic-risk patients due to stent thrombosis concerns. Although our analysis found no significant difference in stent thrombosis, variability across studies reinforces the need for individualized therapy, particularly in elderly or renally impaired patients. The results also emphasize the role of procedural advances—such as radial access and post-procedure Bivalirudin infusions—in improving outcomes. Subgroup analyses showed that Bivalirudin offers consistent bleeding reduction in STEMI patients, aligning with major trials, but does not significantly decrease ischemic events such as stent thrombosis. This highlights the need to balance bleeding benefits against ischemic protection when choosing anticoagulation therapy. In mixed NSTEMI populations, the variability in outcomes may be attributed to differences in antiplatelet regimens and the prevalence of comorbid conditions such as diabetes and renal impairment. These factors likely contribute to the observed heterogeneity (e.g., I^2=81.38% in MACE for NSTEMI). Additionally, variations in procedural techniques and adjunctive therapies further complicate the interpretation of these findings.

Heterogeneity in MACE and NACE outcomes is mainly driven by differences in patient characteristics and procedural protocols, such as GP inhibitor use and dosing variations. Sensitivity analyses support the robustness of the results but highlight the need for more standardized reporting in future studies.

Publication bias—most notable in NACE outcomes—raises concerns about the reliability of pooled results. Funnel plot asymmetry suggests missing or small-study effects that may favor Bivalirudin. Future analyses should include unpublished or registry data to reduce this limitation.

These findings align with ESC and AHA guidelines, which favor Bivalirudin in patients at high bleeding risk—especially in STEMI and radial access procedures where bleeding reduction is most evident. However, because no significant ischemic benefit was observed, Heparin may still be preferable for patients with high ischemic risk, such as those with extensive coronary disease or prior stent thrombosis.

In the EVENT registry analysis by Bangalore et al , patients with NSTEMI or stable ischemic heart disease treated with Bivalirudin had significantly lower bleeding rates without an increase in stent thrombosis or other ischemic events (31).

Independent predictors of MACCEs were analyzed. In univariate logistic regression, bivalirudin treatment (compared to heparin; *P*=0.117) was not linked to an increased risk of MACCEs. Factors associated with higher MACCE risks included age ≥65 years (vs. <65 years; *P*=0.028), a history of hypertension (yes vs. no; *P*=0.034), clinical presentation of SCAD (vs. UA; *P*<0.001), NSTEMI (vs. UA; *P*=0.007), STEMI (vs. UA; *P*=0.001), a CRUSADE score ≥41 (vs. <40; *P*=0.024), emergency surgery (vs. elective surgery; *P*<0.001), and involvement of multiple vessels [vs. a single vessel; *P*=0.044] (30).

Forward stepwise multivariate logistic regression revealed that bivalirudin treatment (vs. heparin; OR 0.386, *P*=0.002) was independently associated with a reduced risk of BARC 3-5 bleeding events. Conversely, a history of diabetes mellitus (yes vs. no; OR 1.805, *P*=0.024), a CRUSADE score ≥41 (vs. <40; OR 2.313, *P*=0.001), emergency surgery (vs. elective surgery; OR 2.379, *P*=0.001), and stent diameter ≥3.5 mm (vs. <3.5 mm; OR 1.635, *P*=0.048) were independently associated with an increased risk of BARC 3-5 bleeding events (30).

Previous meta-analyses have compared bivalirudin against unfractionated heparin in a number of different ways. The study conducted by Liu et al (32) compared bivalirudin to unfractionated heparin in patients with STEMI who were undergoing percutaneous coronary intervention. The study contained seven trials, all of which were included in our own investigation. Bivalirudin was found to be associated with a lower risk of mortality and significant bleeding, as demonstrated by the findings. Anantha-Narayanan et al compared Bivalirudin with unfractionated Heparin across 26 PCI studies involving STEMI, NSTEMI, and angina patients. They found that bivalirudin was associated with reduced major bleeding but a higher risk of stent thrombosis. However, substantial heterogeneity existed due to mixed patient populations and similar GP IIb/IIIa inhibitor use in both groups (33). A Recent study conducted in which they compared bivalirudin to unfractionated heparin in patients who were undergoing transradial coronary procedures [STMEI, NSTEMI, stable and unstable angina](34). The ten-trial analysis showed that Bivalirudin reduced 30-day net adverse effects compared with unfractionated Heparin, though no significant differences were seen in long-term NACE or major bleeding. This meta-analysis is the first to include the BRIGHT-4 trial and the first limited solely to RCTs comparing Bivalirudin monotherapy with Heparin in MI patients. Despite Heparin's wider use due to familiarity and ease, our findings suggest Bivalirudin is a promising alternative and justify further RCTs. Ongoing trials continue to evaluate Bivalirudin in special populations—including elderly patients, those on ECMO, and those undergoing non-culprit artery revascularization—as well as different infusion durations (e.g., the COBER study). Our findings are consistent with previous meta-analyses, including Meng et al, which showed that Bivalirudin reduces major bleeding in elderly PCI patients without affecting MACE. We similarly observed a bleeding reduction in high-risk groups. However, unlike Meng et al, who reported lower NACE in elderly STEMI patients, our overall analysis found no significant NACE difference, indicating that more subgroup-focused research is needed to resolve this discrepancy.

Third, procedural factors such as radial versus femoral access were not analyzed, though these may independently influence bleeding and ischemic outcomes. Future studies should explore how the access-site strategy modulates anticoagulant efficacy.

This meta-analysis has several limitations. Moderate heterogeneity, especially in NACE and stent thrombosis, likely reflects differences in patient populations, procedural techniques, and study designs. Although publication bias was evaluated with Begg's and Egger's tests, these methods may not fully detect bias in small or less rigorously reported studies. Reliance on published data limited access to patient-level information that could better identify subgroups benefiting most from Bivalirudin. Variations in dosing and administration of both anticoagulants may also have influenced outcomes, but were inconsistently reported. Additionally, procedural factors such as radial

vs. femoral access could not be analyzed due to insufficient data, despite their known effect on bleeding and ischemic outcomes. Despite these limitations, the analysis provides a robust comparison of Bivalirudin and Heparin, particularly emphasizing Bivalirudin's bleeding advantage.

Conclusion

This meta-analysis shows that Bivalirudin significantly lowers major bleeding risk compared with Heparin in PCI, but does not improve MACE, mortality, stroke, or stent thrombosis. While it offers a clear safety advantage—particularly in STEMI—its overall clinical effectiveness is similar to Heparin. Moderate heterogeneity highlights the need for further research to identify patient groups that may benefit most from Bivalirudin.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare no conflict of interests.

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