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SYSTEMATIC REVIEW

Differential Use of Glycoprotein IIb/IIIa Inhibitors with Bivalirudin in Patients with STEMI Undergoing PCI: A Systematic Review and Meta-Analysis

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Abstract

Aim The efficacy and safety of bivalirudin when used concurrently with glycoprotein IIb/IIIa inhibitors (GPI) is uncertain. In this systematic review and meta-analysis, we aimed to evaluate the efficacy and safety of bivalirudin versus heparin in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) and to explore the impact of differential use (greater and balanced) of GPI.

Methods Online databases were queried from inception to March 2023 to identify eight randomized controlled trials (n = 22,483) for inclusion. The primary outcomes included all-cause mortality, major bleeding, major adverse cardiovascular events (MACE), and net adverse clinical events (NACE). Secondary efficacy endpoints included cardiac death, reinfarction, stent thrombosis (ST), and stroke. Data were pooled using a random-effects model to derive risk ratios (RRs) and 95% confidence intervals (CIs).

Results When compared to heparin, bivalirudin was associated with a significant reduction in all-cause mortality (RR 0.83; 95% CI 0.72–0.97; $P = 0.02$), major bleeding (RR 0.73; 95% CI 0.57–0.93; $P = 0.01$), cardiac death (RR 0.79; 95% CI 0.66–0.94; $P = 0.01$), and NACE (RR 0.80; 95% CI 0.72–0.89; $P < 0.0001$). However, while the bivalirudin arm showed an increased likelihood of ST in the greater GPI subgroup (RR 1.70; 95% CI 1.13–2.56; $P = 0.01$), it was associated with a decreased likelihood of ST in the balanced GPI subgroup (RR 0.40; 95% CI 0.24–0.65; $P = 0.0003$).

Conclusion Overall, our findings suggest that bivalirudin may be a more efficacious intervention than heparin for reducing certain adverse events in patients with STEMI undergoing primary PCI.

1 Introduction

The recommended protocol for treating ST-segment elevation myocardial infarction (STEMI), as outlined by the National Institute for Health and Care Excellence (NICE) guidelines [1], involves primary percutaneous coronary intervention (PCI), which serves as a non-surgical invasive procedure that focuses on relieving blood flow obstruction in the affected coronary artery. However, PCI is linked with an elevated risk of intra- and post-procedure thrombosis and therefore requires supplementation with antithrombotic therapy [2]. The 2021 update to the NICE guidelines recommends the use of unfractionated heparin (UFH) or bivalirudin, supplemented with a glycoprotein IIb/IIIa inhibitor (GPI) as needed, with bivalirudin showing superior mortality outcomes (both all-cause and cardiac) at 30 days and

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Key Points

Bivalirudin has stirred controversy due to its associated risk of stent thrombosis in the context of primary percutaneous intervention.

This is the first meta-analysis to identify a decreased risk of stent thrombosis associated with bivalirudin when administered alongside similar rates of glycoprotein inhibitors, as compared to heparin.

A prolonged infusion of high-dose bivalirudin, as an alternative to heparin, may be a highly efficacious intervention in patients with ST-elevation myocardial infarction undergoing primary percutaneous intervention.

1 year [1]. Similarly, supported by A-level evidence, the 2015 European Society of Cardiology (ESC) guidelines for PCI management highly endorsed bivalirudin as a class I anticoagulant [3]. However, in subsequent updates to the guidelines in 2017 and 2020, bivalirudin was downgraded to a class IIa and IIb agent, respectively, while maintaining A-level evidence [4, 5]. This change in recommendation is predominantly attributed to the reported elevated risk of stent thrombosis (ST) with bivalirudin compared to UFH, which has raised concerns [3].

Several randomized controlled trials (RCTs) have been conducted to compare the effectiveness of bivalirudin and UFH as anticoagulant therapy during PCI for STEMI. However, these studies have produced conflicting results, particularly concerning major bleeding, all-cause mortality, reinfarction, and ST. For instance, the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial [6] reported a reduction in major bleeding, a 30-day rate of all-cause mortality, and an increase in ST within 24 h with bivalirudin use. However, the findings of this trial were contested by the HEAT-PPCI (How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) trial [7], which found an increase in reinfarction and ST within 24 h, but no reduction in bleeding with bivalirudin. Another recent trial [8], VALIDATE-SWEDEHEART (Bivalirudin Versus Heparin in STEMI and NSTEMI Patients on Modern Antiplatelet Therapy – Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry), found similar outcomes to the HEAT-PPCI study [7], indicating a preference for heparin over bivalirudin, with no significant differences in all-cause mortality, reinfarction, and major bleeding, but an increase in definite ST in the bivalirudin arm. Yet another large-scale trial [9], BRIGHT-4 (Bivalirudin With Prolonged Full-Dose Infusion During Primary PCI Versus Heparin), demonstrated that bivalirudin reduced major bleeding and the 30-day rate of all-cause mortality, with no significant differences observed in reinfarction.

Given the discrepancies in previous trials, two previous meta-analyses were conducted to evaluate the efficacy of bivalirudin. However, these analyses yielded conflicting findings, especially regarding all-cause mortality [10, 11]. Moreover, there is a growing concern regarding the potential disparities in the efficacy of bivalirudin with the differential use of GPI. To address these inconsistencies, we sought to conduct a pre-determined subgroup meta-analysis to provide a holistic picture and compare the safety and efficacy of bivalirudin versus heparin with differential use (greater or balanced) of GPI in patients with STEMI undergoing PCI and further analyzed the outcomes of elderly patients and 1-year follow-up.

2 Methods

2.1 Data Sources and Search Strategy

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. A comprehensive search was conducted using the Cochrane CENTRAL, PubMed/MEDLINE, and SCOPUS databases, from inception to March 2023. Bibliographies of the included articles and previous meta-analyses were also screened for any relevant articles. The search was not limited by publication status or language. The search terms included relevant PubMed MeSH terms and related text terms, such as bivalirudin, heparin, ST-elevation myocardial infarction, primary percutaneous coronary intervention, and randomized trial. The detailed search strategy is provided in Supplementary Table S1 (see the electronic supplementary material).

2.2 Study Selection and Eligibility Criteria

All articles retrieved from the systematic search were exported to the EndNote reference library, version X8.1 (Clarivate Analytics), wherein duplicates were removed. The screening process involved independent evaluation and selection of studies by two authors (SHF and MHS), with discrepancies resolved by a third author (HM). Eligible studies were required to meet the following inclusion criteria: (1) being an RCT with human participants; (2) administering bivalirudin versus heparin monotherapy to a study population of patients with STEMI undergoing PCI; and (3) reporting outcomes of interest related to the safety and efficacy. We excluded the studies with overlapping publications unless new data were presented in pre-specified subgroup analyses.

In addition, studies were also excluded if thrombolysis was done prior to randomization. Observational studies, reviews, conference abstracts, editorials, case reports, and case series were also excluded.

2.3 Data Extraction

Two authors (SAS and HM) conducted independent evaluations of the data and supplementary materials, with any conflicts resolved through consultation with a third author (SHF). The following data were extracted from included studies: year of publication, number of participants, patients' baseline characteristics, follow-up duration, GPI utilization rate, medication prescriptions at discharge, and outcomes related to efficacy and safety. The study's primary efficacy and safety endpoints consisted of the short-term (< 180 days) incidence rates of all-cause mortality, major adverse cardiovascular events (MACE), net adverse clinical events (NACE), and protocol-defined major bleeding. The secondary endpoints comprised the short-term (< 180 days) incidence rates of cardiovascular death, reinfarction, stroke, and definite ST. The definitions of all endpoints are presented in Supplementary Table S2 (see the electronic supplementary material).

2.4 Quality Assessment

Quality assessment was conducted by two authors (SHF and KB). The risk of bias in each trial was evaluated using the Cochrane Risk of Bias tool for RCTs [13]. Trials were rated against the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. The result of the quality screening of each study was expressed as a low, high, or unclear risk for each type of bias. In the case of disagreement between the two authors, a third author (SAS) was consulted.

2.5 Statistical Analysis

Two authors (SAS and HM) performed statistical analysis using Review Manager (RevMan version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A Mantel-Haenszel random-effects model was employed to amalgamate the results of all studies. A P value was considered significant when it was ≤ 0.05. We used risk ratios (RRs) with 95% confidence intervals (CIs) to measure the dichotomous outcomes. The statistical heterogeneity was assessed using the I^2 index where a value of < 50%, 50–75%, and > 75% were considered as low, moderate, and high heterogeneity, respectively [14]. In the case of heterogeneity > 50%, we conducted the sensitivity analysis by employing the leave-one-out analysis to identify the trial causing significant heterogeneity. Subgroup and sensitivity analyses were conducted to explore potential sources of inconsistency in both the short-term (≤ 180 days) and long-term (≥ 1-year follow-up) outcomes, as well as in the elderly (≥ 65 years of age). In the short-term outcomes, the rates of GPI use were compared between the bivalirudin and heparin treatment arms. Subgroups were defined based on the relative rates of GPI utilization in each arm. Specifically, when the GPI usage rate was higher in the bivalirudin arm compared to the heparin arm, it was referred to as the "greater GPI subgroup." Conversely, when the rates of GPI use were similar between the two arms, it was referred to as the "balanced GPI subgroup." Potential publication bias was evaluated by creating a funnel plot for the short-term outcome of all-cause mortality (Fig. S2; see the electronic supplementary material).

3 Results

3.1 Study Characteristics and Baseline Demographics

A preliminary search produced 1253 possibly pertinent articles, of which 753 remained after eliminating duplicates. A total of eight studies [6–9, 15–18] comprising a total trial population of 22,483 patients (n = 11,240 in the bivalirudin arm and n = 11,243 in the heparin arm), met the inclusion criteria and had no exclusion criteria. The literature search is summarized by the PRISMA flowchart in Figure 1. Study characteristics and the patient baseline characteristics are presented in Table 1. All eight studies [6–9, 15–18] included in our meta-analysis reported a low risk of bias. The only consistent bias among the included studies was the blinding of participants and personnel (performance bias) (Fig. S2 and Table S3; see the electronic supplementary material).

3.2 Clinical Outcomes

3.2.1 All-Cause Mortality

All eight studies included data on all-cause mortality, and a statistically significant reduction in its incidence was observed in the bivalirudin treatment arm in comparison to the heparin treatment arm (RR 0.83; 95% CI 0.72–0.97; P = 0.02; I^2 = 3%) (Fig. 2A). At greater GPI, a significant reduction in the incidence of all-cause mortality was observed between the two treatment arms (RR 0.73; 95% CI 0.58–0.93; P = 0.009; I^2 = 0%) (Fig. 2A). However, at balanced GPI, no significant difference in the incidence of all-cause mortality was observed between the two arms (RR 0.92; 95% CI 0.74–1.15; P = 0.46; I^2 = 19%) (Fig. 2A).

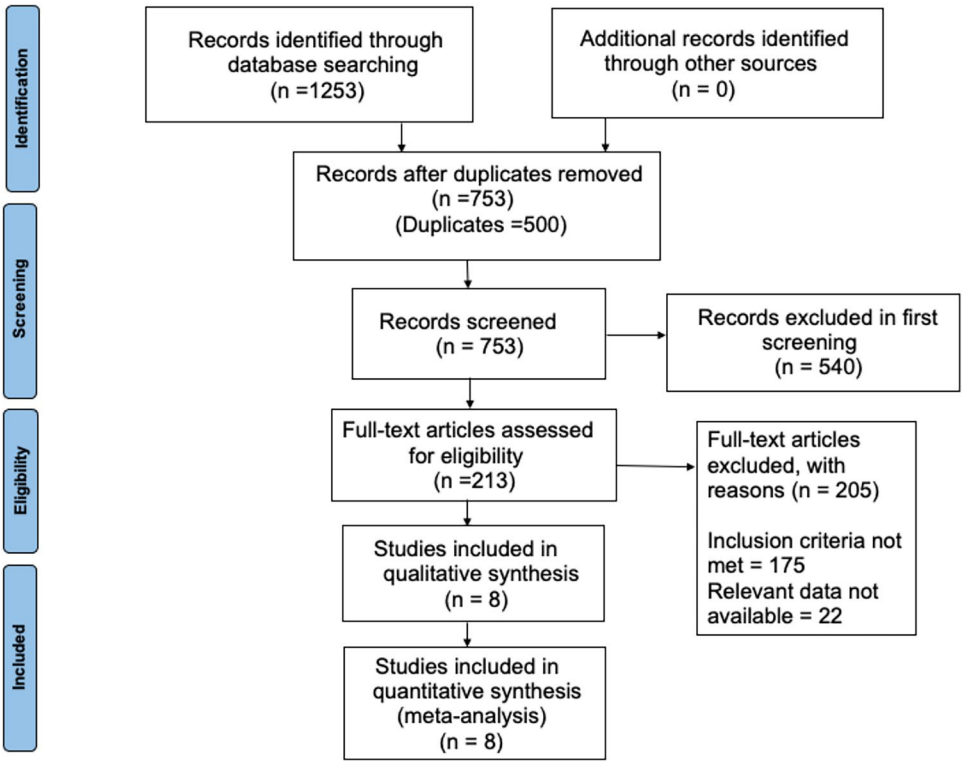


Fig. 1 PRISMA flow diagram. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

In the long-term subgroup, there was no significant difference in the risk of all-cause mortality between the bivalirudin and heparin arms (RR 0.79; 95% CI 0.47–1.34; $P = 0.39$; $I^2 = 88\%$) (Fig. 2B). Given the high heterogeneity associated with this outcome and subgroup, a sensitivity analysis was conducted, whereby we excluded the HEAT-PPCI trial [7]. As a result, a significant reduction in the risk of all-cause mortality along with a reduction in heterogeneity from an initial I^2 value of 88% to 19% was observed (RR 0.61; 95% CI 0.48–0.78; $P < 0.0001$; $I^2 = 19\%$) (Fig. S3; see the electronic supplementary material).

Moreover, there was no significant difference in the risk of all-cause mortality between the bivalirudin and heparin arms in the elderly population (RR 0.90; 95% CI 0.66–1.22; $P = 0.49$; $I^2 = 37\%$) (Fig. S4).

3.2.2 Major Bleeding

Data for major bleeding was reported by all eight studies analyzed, and the results showed a significant difference in the incidence of major bleeding events between the bivalirudin and heparin arms (RR 0.73; 95% CI 0.57–0.93; $P = 0.01$; $I^2 = 75\%$) (Fig. 3A). The incidence of major bleeding in the bivalirudin arm was found to be significantly lower in the greater GPI subgroup (RR 0.54; 95% CI 0.44–0.66; $P < 0.00001$; $I^2 = 10\%$) (Fig. 3A). At balanced GPI, the incidence of major bleeding was not significantly different between the bivalirudin and heparin arms (RR 0.97; 95% CI 0.84–1.11; $P = 0.64$; $I^2 = 0\%$) (Fig. 3A). While the overall heterogeneity was deemed high ($I^2 = 75\%$), heterogeneity was low in both subgroups (Fig. 3A). Therefore, no sensitivity analysis was conducted for this outcome.

Similarly, in the elderly population, the bivalirudin arm exhibited a significantly lower incidence of major bleeding in comparison to the heparin arm (RR 0.73; 95% CI 0.54–0.99; $P = 0.04$; $I^2 = 44\%$) (Fig. S5; see the electronic supplementary material).

3.2.3 MACE

Data for MACE, reported by all eight studies, yielded non-significant results, establishing that bivalirudin was non-superior to heparin in reducing the risk of cardiovascular complications (RR 0.90; 95% CI 0.81–1.01; $P = 0.09$; $I^2 = 0\%$) (Fig. 3B). Furthermore, no significant difference was observed in the incidence of MACE between the bivalirudin and heparin arms in both the greater GPI subgroup (RR 0.95; 95% CI 0.82–1.10; $P = 0.51$; $I^2 = 0\%$) and balanced GPI subgroup (RR 0.85; 95% CI 0.71–1.01; $P = 0.06$; $I^2 = 0\%$) (Fig. 3B).

Similarly, in the long-term subgroup, there was no significant difference in the risk of MACE between the bivalirudin and heparin arms (RR 0.98; 95% CI 0.87–1.10; $P = 0.68$; $I^2 = 0\%$) (Fig. 3C).

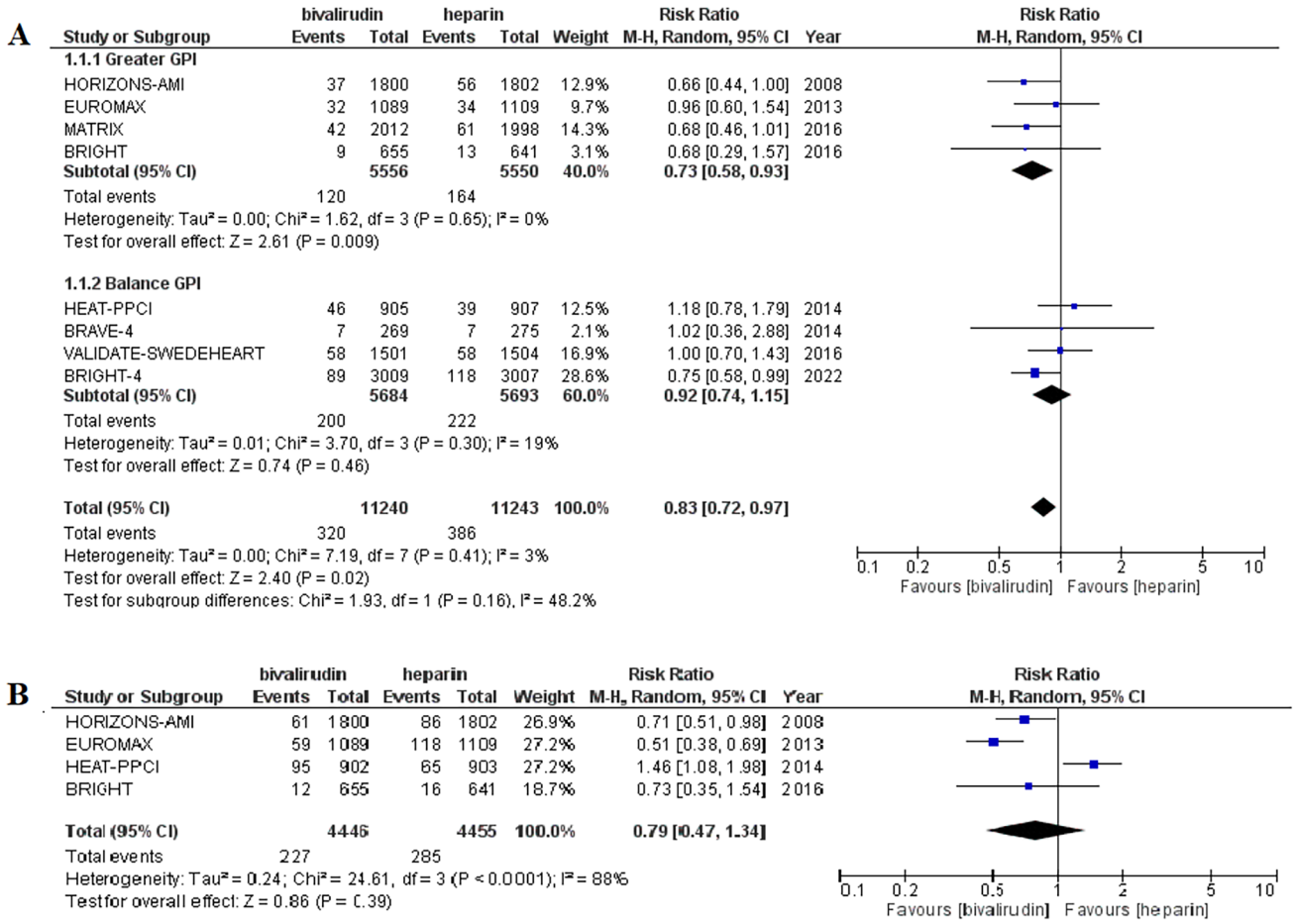


Fig. 2 **A** Forest plot of all-cause mortality events in the short term. **B** Forest plot of all-cause mortality events in the long term. *CI* confidence interval, *GPI* glycoprotein IIb/IIIa inhibitor

3.2.4 NACE

NACE was documented in seven trials. The use of bivalirudin showed a significant reduction in the incidence of NACE when compared to the use of heparin (RR 0.80; 95% CI 0.72–0.89; $P < 0.0001$; $I^2 = 25\%$) (Fig. 4A). At greater GPI, the incidence of NACE was significantly lower in the bivalirudin arm compared to the heparin arm (RR 0.76; 95% CI 0.68–0.86; $P < 0.00001$; $I^2 = 0\%$) (Fig. 4A). However, at balanced GPI, there was no significant difference in the incidence of NACE between the bivalirudin and heparin arms (RR 0.87; 95% CI 0.73–1.05; $P = 0.14$; $I^2 = 36\%$) (Fig. 4A).

In the long-term subgroup, the bivalirudin arm also exhibited a significantly lower incidence of NACE compared to the heparin arm (RR 0.86; 95% CI 0.76–0.98; $P = 0.03$; $I^2 = 38\%$) (Fig. 4B).

Moreover, in the elderly population, there was no significant difference in the incidence of NACE between the bivalirudin and heparin arms (RR 0.88; 95% CI 0.70–1.11; $P = 0.28$; $I^2 = 45\%$) (Fig. S6; see the electronic supplementary material).

3.2.5 Cardiac Death

Cardiac death was reported in six studies. Bivalirudin was associated with a significant decrease in the incidence of cardiac death compared to heparin (RR 0.79; 95% CI 0.66–0.94; $P = 0.01$; $I^2 = 0\%$) (Fig. 5A). At greater GPI, the incidence of cardiac death was significantly lower in the bivalirudin arm compared to the heparin arm (RR 0.69; 95% CI 0.51–0.94; $P = 0.02$; $I^2 = 0\%$) (Fig. 5A). However, at balanced GPI, there was no significant difference in the incidence of cardiac death

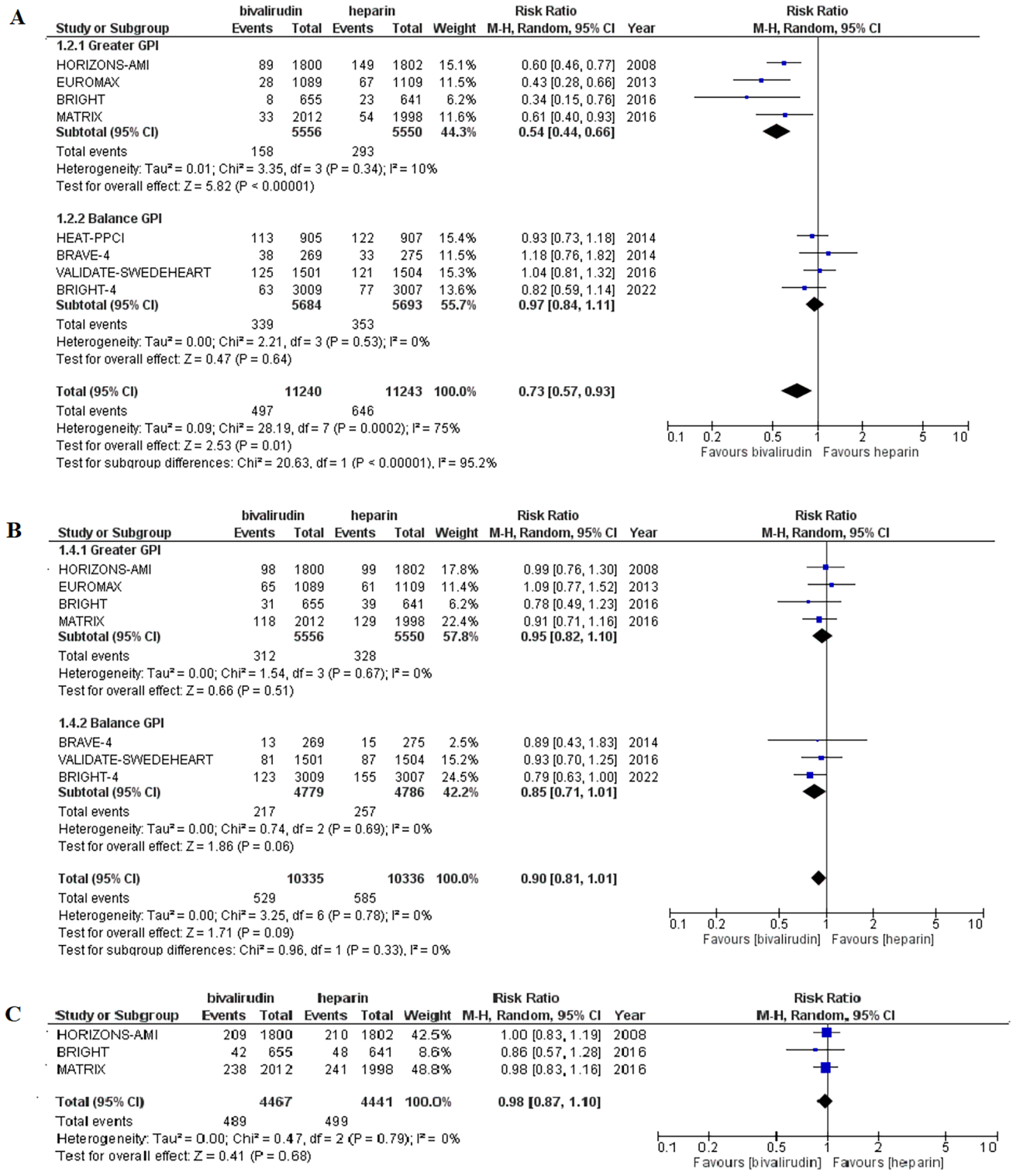


Fig. 3 **A** Forest plot of major bleeding events in the short term. **B** Forest plot of MACE in the short term. **C** Forest plot of MACE in the long term. *CI* confidence interval, *GPI* glycoprotein IIb/IIIa inhibitor, *MACE* major adverse cardiovascular events

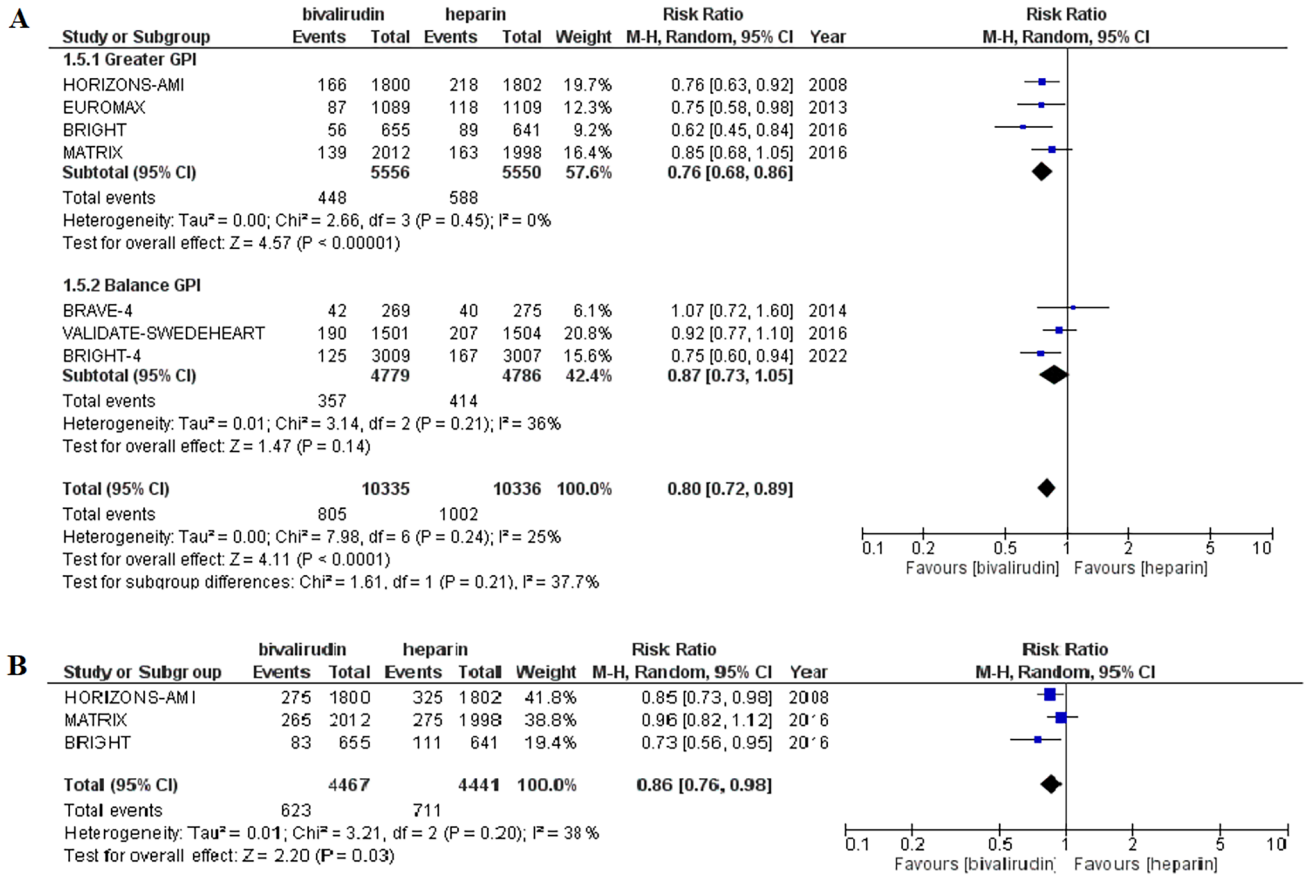


Fig. 4 **A** Forest plot of major NACE events in the short term. **B** Forest plot of NACE events in the long term. *CI* confidence interval, *GPI* glycoprotein IIb/IIIa inhibitor, *NACE* net adverse clinical events

between the bivalirudin and heparin arms (RR 0.85; 95% CI 0.68–1.06; $P = 0.14$; $I^2 = 0\%$) (Fig. 5A).

Similarly, in the long-term subgroup, the incidence of cardiac death did not differ significantly between the bivalirudin and heparin arms (RR 0.85; 95% CI 0.56–1.31; $P = 0.47$; $I^2 = 73\%$) (Fig. 5B). Given the considerable heterogeneity observed in the long-term subgroup, a sensitivity analysis was performed which excluded the HEAT-PPCI trial [7], resulting in a significant reduction in heterogeneity from $I^2 = 73\%$ to $I^2 = 35\%$ (RR 0.71; 95% CI 0.51–1.01; $P = 0.06$; $I^2 = 35\%$) (Fig. S7; see the electronic supplementary material).

3.2.6 Reinfarction

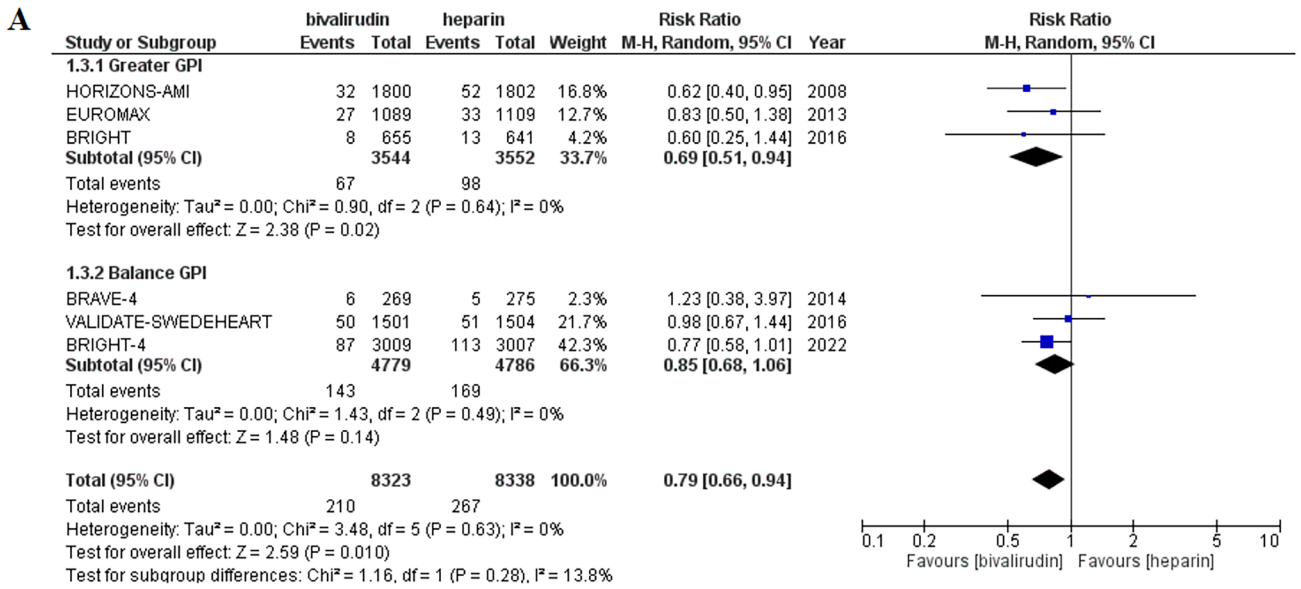
All eight studies reported reinfarction. Overall, no significant difference was observed in the risk of reinfarction between the bivalirudin and heparin arms (RR 1.13; 95% CI 0.83–1.55; $P = 0.43$; $I^2 = 48\%$) (Fig. 5C). The incidence of reinfarction did not significantly differ between the bivalirudin and heparin arms in both the greater GPI subgroup (RR 1.22; 95% CI 0.94–1.56; $P = 0.13$; $I^2 = 0\%$) (Fig. 5C) and balanced GPI subgroup (RR 1.08; 95% CI 0.55–2.14; $P = 0.82$; $I^2 = 70\%$) (Fig. 5C).

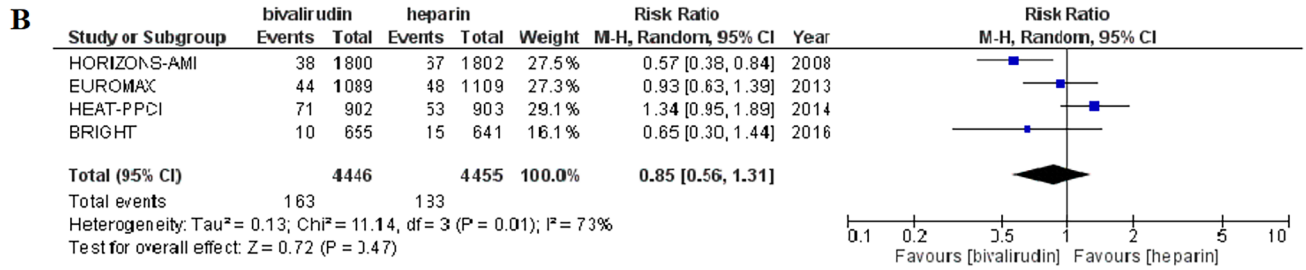
3.2.7 Stroke

Data for stroke was provided by all eight studies. Overall, no significant difference in the incidence of stroke was observed between the bivalirudin and heparin arms (RR 0.79; 95% CI 0.56–1.12; $P = 0.19$; $I^2 = 13\%$) (Fig. 6A), as well as in the greater GPI (RR 0.69; 95% CI 0.41–1.19; $P = 0.19$; $I^2 = 18\%$) and balanced GPI subgroups (RR 0.87; 95% CI 0.53–1.43; $P = 0.58$; $I^2 = 23\%$) (Fig. 6A).

3.2.8 Stent Thrombosis

Among the eight studies that reported ST, no significant difference was observed in the incidence of ST between the bivalirudin and heparin arms (RR 1.14; 95% CI 0.59–2.20; $P = 0.70$; $I^2 = 80\%$) (Fig. S8; see the electronic supplementary material). A sensitivity analysis was conducted to address the high heterogeneity of this outcome, whereby the HEAT-PPCI trial [7] was excluded, resulting in a negligible





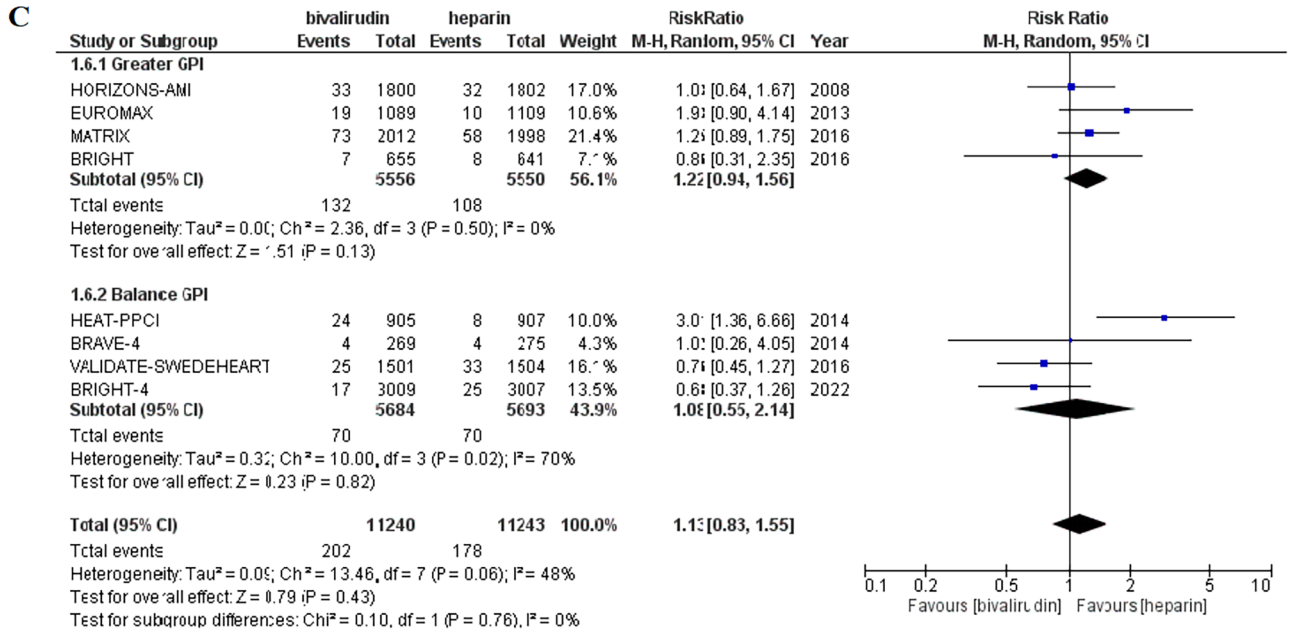


Fig. 5 **A** Forest plot of cardiac death events in the short term. **B** Forest plot of cardiac death events in the long term. **C** Forest plot of reinfarction events in the short term. *CI* confidence interval, *GPI* glycoprotein IIb/IIIa inhibitor

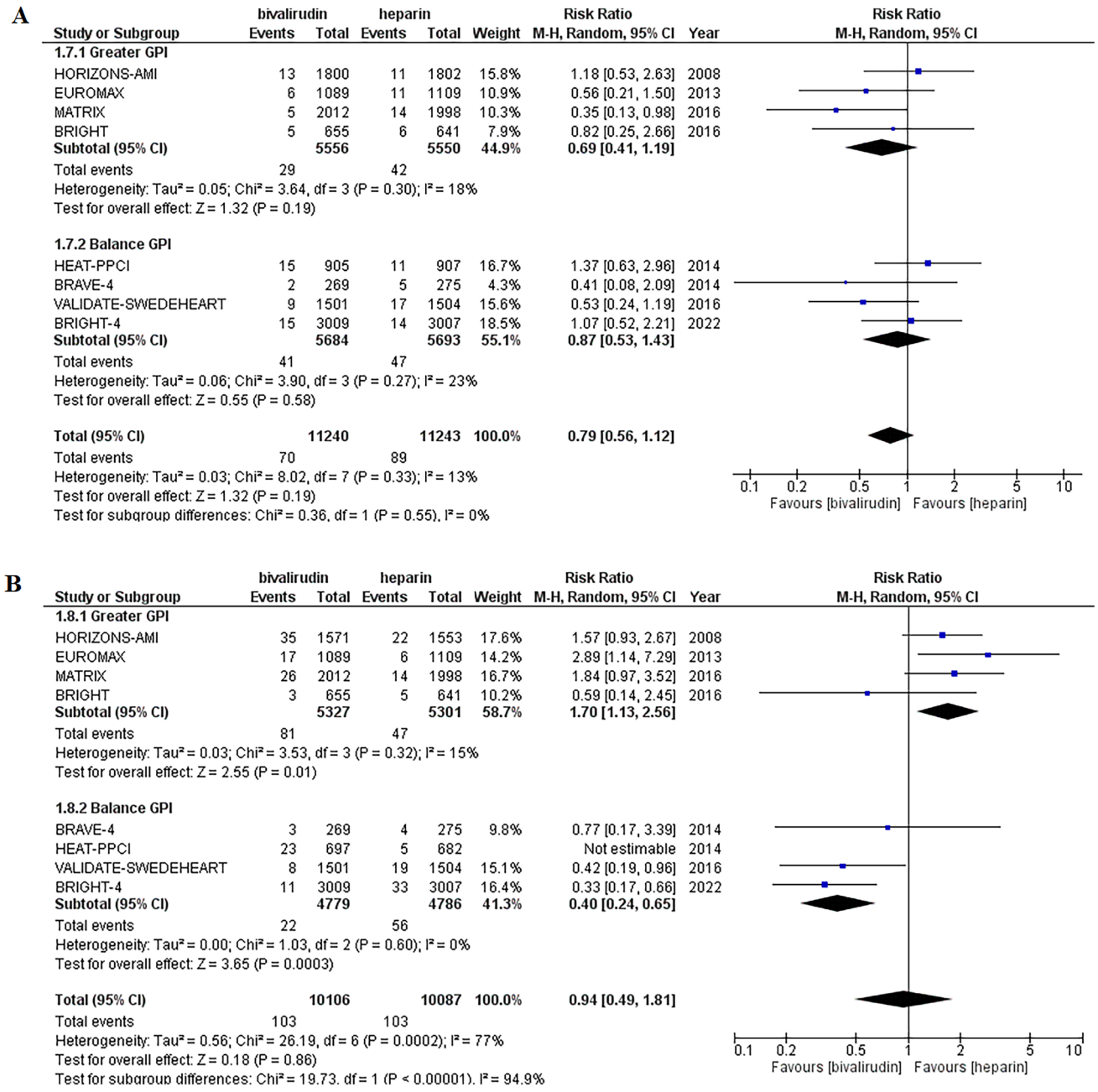


Fig. 6 **A** Forest plot of stroke events in the short term. **B** Forest plot of stent thrombosis events in the short term. *CI* confidence interval, *GPI* glycoprotein IIb/IIIa inhibitor

decrease in heterogeneity from $I^2 = 80\%$ to $I^2 = 77\%$ (RR 0.94; 95% CI 0.49–1.81; $P = 0.86$; $I^2 = 77\%$) (Fig. 6B). Following the sensitivity analysis, it was concluded that the bivalirudin arm exhibited an increased likelihood of ST when compared to the heparin arm at greater GPI (RR 1.70; 95% CI 1.13–2.56; $P = 0.01$; $I^2 = 15\%$) (Fig. 6B). However, at balanced GPI, the likelihood of ST was significantly decreased in the bivalirudin arm (RR 0.40; 95% CI 0.24–0.65; $P = 0.0003$; $I^2 = 0\%$) (Fig. 6B).

4 Discussion

The findings of our comprehensive meta-analysis, based on eight RCTs [6–9, 15–18] consisting of 22,483 patients, demonstrate that in the short term, bivalirudin is associated with a statistically significant reduction in the risk of all-cause mortality, major bleeding, cardiac death, and NACE. with subgroup analyses showing a more pronounced benefit of bivalirudin in the greater GPI subgroup compared to the

balanced GPI subgroup. Additionally, we found a significant reduction in the risk of all-cause mortality and NACE in the long term. Moreover, outcomes for elderly patients were inconclusive, with the exception of major bleeding.

Two meta-analyses, namely one conducted by Capodanno et al. [10] in 2016 and the other by Liu et al. in 2020 [11], investigated the relationship between bivalirudin and heparin. Capodanno et al. [10] found that bivalirudin was linked to comparable mortality rates and a lower risk of major bleeding, but also an alarming increase in the risk of acute ST. In contrast, Liu et al. [11] found that bivalirudin was associated with a reduced risk of all-cause mortality and major bleeding compared to heparin, in both the greater GPI subgroup and overall analysis. However, their study also identified an increased risk of reinfarction and ST associated with bivalirudin administration. Our analysis not only strengthens the existing evidence for the effectiveness of bivalirudin in reducing the risk of major bleeding and all-cause mortality but also reveals a new finding that bivalirudin reduces the risk of cardiac death and NACE.

The trials included in the greater GPI subgroup analysis have consistently demonstrated that bivalirudin treatment is associated with a significantly lower incidence of major bleeding events compared to heparin. For instance, the EUROMAX [15] and BRIGHT [17] trials, which were included in the greater GPI subgroup and involved high-dose heparin monotherapy, found that the use of bivalirudin was associated with a significant decrease in major bleeding. However, in the HEAT-PPCI trial [7], which was included in the balanced GPI subgroup and used a lower dose of heparin, no such association was observed. This relationship indirectly suggests that administering heparin in high doses significantly increases the risk of bleeding complications as compared to bivalirudin [19–22]. Our overall findings indicate that bivalirudin is associated with a decreased risk of major bleeding compared to heparin, which is likely the main mechanism by which bivalirudin improves mortality and NACE. A possible explanation behind the reduced risk of major bleeding associated with bivalirudin administration is likely due to its direct thrombin inhibition, which differs from the non-specific targeting mechanism of heparin [23–25].

While bivalirudin use in the greater GPI subgroup has consistently shown a reduced risk of major bleeding events compared to heparin, bivalirudin's association with ST has varied across subgroups. More specifically, our analysis showed that bivalirudin use in the greater GPI subgroup was associated with an increased likelihood of ST, a finding consistent with a previous meta-analysis conducted by Liu et al. [11]. However, in the balanced GPI subgroup, bivalirudin was associated with a significant decrease in the risk of ST. This discrepancy can be explained by the variations in bivalirudin regimens employed across the trials analyzed. For example, the EUROMAX trial [15], included in the greater GPI subgroup, utilized a prolonged, reduced-dose infusion of bivalirudin and third-generation P2Y12 inhibitors that failed to reduce the risk of ST in the bivalirudin arm. In contrast, the VALIDATE-SWEDEHEART [8] and BRIGHT-4 [9] trials, the first two trials demonstrating a reduced risk of ST in the bivalirudin arm, employed a prolonged infusion of high-dose bivalirudin (0.75 mg/kg followed by an infusion of 1.75 mg/kg × h). Bivalirudin's shorter half-life of approximately 25 min and reversible binding to thrombin may potentially allow for more rapid normalization of coagulation following PCI, resulting in a lower risk of thrombotic events [26, 27]. Further supporting evidence comes from a post hoc analysis of the EUROMAX trial [28], which demonstrated that administering a post-procedure bivalirudin infusion at the PCI dose for a median duration of 4.5 h effectively eliminated the acute risk of ST following PCI. Based on our analysis, a prolonged high-dose infusion of bivalirudin may be a viable solution to address the safety concerns associated with this drug. However, further research is necessary to establish an optimal dosing strategy that maximizes the benefits of bivalirudin in reducing the risk of ST while minimizing the potential for bleeding complications. Another possible explanation for the increased risk of ST in the greater GPI subgroup is the complexity of lesions or heightened ischemic risk factors present in the patients at baseline. For instance, the EUROMAX [15] and HORIZONS-AMI [6] trials stated that treatment choices were influenced by individual patient characteristics and procedural risks. Therefore, further trials are suggested to adopt a more rigorous approach, incorporating randomization and addressing baseline differences.

Our analysis did not reveal any significant difference between the two reinfarction groups. This may be attributed to variations in the definition of reinfarction used across the studies, as presented in Supplementary Table S2 (see the electronic supplementary material). While all the trials included in our analysis employed a rise and/or fall in cardiac biomarkers to define reinfarction, certain studies [7, 15] also included additional diagnostic criteria such as imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities (Table S2). The variability in the diagnostic criteria used across the trials could potentially result in inconsistencies in the reported incidence of reinfarction, which in turn may have affected the statistical significance of the trial outcomes.

The long-term administration of bivalirudin was found to be associated with significant reductions in all-cause mortality and NACE in this analysis, which is consistent with the findings of a previous meta-analysis from 2021 [29]. However, it is important to note that the all-cause mortality outcome was sensitive to the HEAT-PPCI trial [7] and was therefore excluded from the analysis. Despite this, the

overall findings suggest that bivalirudin is associated with improved long-term outcomes. Notably, the HORIZONS-AMI trial [30] showed that after 1 year of follow-up, the rates of ST were similar in the two treatment arms. This suggests that any possible harm related to bivalirudin (such as the initial increase in ST in the bivalirudin group) was balanced out by a subsequent decrease in ST between 24 h and 1 year when compared to the control group. Although the studies included in the long-term subgroup suggest a sustained or improving risk–benefit profile of bivalirudin over time, there is still a need for more large-scale RCTs with adequate statistical power and prolonged follow-up to comprehensively address the remaining uncertainties associated with bivalirudin and establish a more definitive understanding of its long-term efficacy and safety profile.

4.1 Strengths and Limitations

This study possesses several strengths that support the validity of our findings. While previous meta-analyses [10, 11, 29] have focused exclusively on the pharmacologic interventions on patients from a single population type, our analysis sought to evaluate a wider range of population sub-classifications to assess potential differences in outcomes across patient subgroups. To our knowledge, our meta-analysis is the first to differentiate findings according to follow-up times, patient populations, and interventions - essentially combining the objectives of various individual meta-analyses into one overarching analysis. Our updated meta-analysis includes two additional large-scale RCTs [8, 9] with frequent radial artery access, which is preferred over femoral access due to a lower risk of bleeding complications [31]. The inclusion of these high-powered studies has allowed us to identify new significant associations that were not found in previous meta-analyses [10, 11, 29]. Of particular importance, our analysis is the first to identify a decreased ST risk associated with bivalirudin use in the balanced GPI subgroup. This finding directly addresses a major resistance factor to the adoption of bivalirudin, which is its reported elevated risk of ST. Furthermore, the high quality of the studies included in our meta-analysis, as evidenced by the low risk of bias assessment (Table S3), adds strength to our findings. In addition, the absence of publication bias in our analysis suggests that the selective reporting of studies did not influence our results. Lastly, mild-to-moderate heterogeneity was observed for a few of the endpoints, which were addressed with the removal of single studies in several of the major outcomes – resulting in a more consistent and reliable estimate.

Some limitations should be considered when interpreting our findings. Variations in the design of studies (as presented in baseline Table 1) and in the definitions of endpoints (as presented in Table S2) are typical limitations of all meta-analyses [24, 32]. All of the studies included in this meta-analysis are subject to the limitations of an open-label design and a predominantly Western setting. These factors may restrict the applicability of our findings to other regions or settings. However, we recommend that future trials explore non-Western regions and healthcare settings to expand the current scope of literature. Moreover, we conducted a study-level meta-analysis; hence, significant variations across the selected studies were not taken into consideration. An individual patient-level meta-analysis would have yielded results of greater reliability in this regard as factors such as dosage, demographics, etc. could have been taken into account [25]. For these reasons, the generalizability of our findings may be limited by the demographic and clinical heterogeneity of the included studies. In addition, it is worth noting that all the trials included in our analysis were multicenter, except for the HEAT-PPCI trial [7], which was unique in randomly assigning a nearly all-inclusive patient population, which limits its generalizability. As a result, some of our results were heavily influenced by this study. To address this potential influence, we conducted a sensitivity analysis that excluded the HEAT-PPCI trial [7]. This exclusion resulted in a substantial decrease in heterogeneity and led to a notable impact on our findings. Nonetheless, it is important to exercise caution when extrapolating our results to other patient populations or clinical settings. Specifically, our analysis was constrained by the limited availability of data for the elderly and long-term subgroups. Additionally, some of the studies included in our analysis did not have an elderly subgroup, while others that did, failed to distinguish between patients with STEMI and non-ST-elevation myocardial infarction (NSTEMI). Thus, the lack of data on the elderly subgroup may have substantially influenced our elderly subgroup analysis. Overall, while subgroup analyses can provide valuable insights into heterogeneity and treatment effects within specific subpopulations, it is important to acknowledge their inherent limitations such as the potential for increased type I errors and data-driven subgroup selection with less power [33, 34]. Additionally, it is crucial to consider baseline health characteristics of patients within these subgroups. For example, the observed increased risk of ST in the greater GPI subgroup could be indicative of more complex underlying conditions, such as severe lesions or elevated ischemic risk factors. Thus, it may be useful to view subgroups through an exploratory and hypothesis-generating lens, rather than as definitive evidence of effect modification.

Table 1 Baseline characteristics

Trial treatment	BRIGHT-4 (2022)		VALIDATE-SWEDEHEART (2016)		BRIGHT (2016)		MATRIX (2016)		HEAT-PPCI (2014)		BRAVE-4 (2014)		EUROMAX (2013)		HORIZONS-AMI (2008)	
	BIV ($n = 3009$)	HEP ($n = 3007$)	BIV ($n = 1501$)	HEP ($n = 1504$)	BIV ($n = 655$)	HEP ($n = 641$)	BIV ($n = 2012$)	HEP ($n = 1998$)	BIV ($n = 905$)	HEP ($n = 907$)	BIV ($n = 271$)	HEP ($n = 277$)	BIV ($n = 1089$)	HEP ($n = 1109$)	BIV ($n = 1800$)	HEP ($n = 1802$)
Short-term FU (days)	30		180		30		30		30		30		30		30	
Mean age (years)	60.5	60.6	68	67	57.1	57.8	63.9	63.9	62.9	63.6	66	58	61	62	59.8	60.7
Male (%)	78.1	78.9	72.6	72.2	85.2	82.5	77	77.3	71	73	76	79	74.7	77.6	77.1	76.1
DM (%)	22.2	23.2	13.5	14.3	22.7	16.5	18	17.8	13	15	17	15	11.7	15.3	15.6	17.3
HT (%)	52	50.5	45.9	46.7	39.8	40.9	57.2	54.3	40	43	66	64	42.2	45.5	51.8	55.2
Hyperlipidemia (%)	–	–	22.7	22.7	35.3	38.5	38.9	39.3	37	28	57	51	36.6	37.6	43.4	42.7
Current smoker (%)	45.2	46.3	27.8	27.9	63.8	59.8	40.8	40.8	42	43	–	–	41.6	42.6	46.9	45
Prior MI (%)	6.2	6.6	12.7	11.8	3.2	3	9.3	9.8	14	10	8	11	7.4	10.2	10.4	11.4
Prior PCI (%)	6.2	6.2	12.1	10.5	5	4.2	9.9	9.3	8	6	–	–	8.9	9.7	10.4	11
CrCl < 60 mL/min (%)	7	6.8	–	–	9.5	10.6	15.4	15.3	–	–	–	–	14.7	16.5	15.8	17.4
Stenting	90.7	90.6	–	–	96.7	96.7	91	90.8	93	92	–	–	92	91.4	90	88
TFA	6.4	7.4	–	–	22	22	50	50	19	28	–	–	52.2	52.2	93.8	94.1
TRA	93.6	92.6	–	–	78.1	78.1	50	50	80	82	–	–	47.7	46.3	6.2	5.9
ASA at discharge (%)	–	–	93.9	93.2	98.3	98.3	96.3	96.5	94	95	–	–	91.8	91.3	98.1	97.1
P2Y12i at discharge (%)	–	–	95	95.3	98.3	98.3	90.4	91.3	89	88	98.3	97.3	86.1	84.9	93.7	92.7
Statin at discharge (%)	–	–	94.3	95.1	88.7	91.3	74.7	71.8	90	91	96.3	96.1	88.9	89.9	93.7	93.8
BB at discharge (%)	–	-	88.9	89.9	73.7	71.3	83.4	83.7	86	87	97.5	97.2	86.7	86.3	79.5	90.2
ACEi/ARB at discharge (%)	-	-	88.4	88.1	54.4	56.2	81.8	79.5	84	86	95.3	91.3	65.9	63.9	79.5	82.2

ACEi angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ASA* aspirin (acetylsalicylic acid), *BB* beta-blocker, *BIV* bivalirudin, *CrCl* creatine clearance, *DM* diabetes mellitus, *FU* follow-up, *HEP* heparin, *HT* hypertension, *MI* myocardial infarction, *P2Y12i* purinergic P2Y12 receptor inhibitor, *PCI* percutaneous coronary intervention, *TFA* transfemoral access, *TRA* transradial access

5 Conclusions

Our meta-analysis indicates that bivalirudin is a promising alternative to heparin as an anticoagulant for patients with STEMI undergoing primary PCI. Its use is associated with a lower risk of major bleeding, cardiac death, all-cause mortality, and NACE in the short term, and a reduced risk of cardiac death and NACE in the long term. When considering the clinical applications of bivalirudin, it is imperative to recognize the disparity in outcomes that occur as a result of differences in dosing regimens. While the greater GPI subgroup shows an increase in the risk of ST with bivalirudin use, the balanced GPI subgroup exhibits a significant reduction in the risk of ST. Therefore, a prolonged infusion of high-dose bivalirudin may be highly successful in reducing ST in certain contexts without adversely influencing other safety outcomes. Given the variations in study protocols and the continued evolution of techniques and adjunct pharmacotherapy, further large-scale randomized trials with long-term follow-up are necessary to support these claims.

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Declarations

Conflicts of interest Hasan Mushahid, Syeda Ayesha Shah, Syed Husain Farhan, Muhammad Hamza Shuja, Kyle Balasingam, Asad Ali, Ishaque Hameed, Kamran Akram, Shayan Mushahid, and Muhammad Shariq Usman declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

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Authors' contributions **HM**: Conceptualization; investigation; formal analysis; writing – original draft; writing – review and editing. **SAS**: Conceptualization; investigation; formal analysis; writing – original draft. **SHF**: Formal analysis; methodology. **MHS**: Methodology; writing – original draft. **KB**: Methodology; writing – original draft. **AA**: Writing – review and editing. **IH**: Resources; writing – review and editing; project administration. **KA**: Project administration; supervision. **SM**: Project administration; supervision. **MSU**: Methodology; writing – review and editing; project administration.

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