Bivalirudin Versus Heparin During Percutaneous Coronary Intervention in Patients With Acute Myocardial Infarction

Hiten Patel[a, b], Rana Garris[b, e], Suchit Bhutani[c], Priyank Shah[d], Upamanyu Rampal[b],
Rahul Vasudev[b], Gabriel Melki[b], Bader Abu Ghalyoun[b], Hartaj Virk[b],
Mahesh Bikkina[b], Fayez Shamoon[b]

Abstract

Background: The aim of the study was to compare the efficacy and safety of bivalirudin versus unfractionated heparin (UFH) in patients with acute myocardial infarction who undergo percutaneous coronary intervention (PCI). Earlier trials comparing bivalirudin and UFH during PCI demonstrated that bivalirudin caused less bleeding with more stent thrombosis. Since then, adjunct antiplatelet strategies have evolved. Improved upstream platelet inhibition with potent P2Y12 inhibitors decreased the need for routine glycoprotein IIb/IIIa inhibitor (GPI), resulting in similar outcomes among UFH and bivalirudin. Therefore, the role of bivalirudin in modern PCI practices is questionable.

Methods: We utilized Cochrane Review Manager (RevMan) 5.3 to perform a meta-analysis of seven randomized controlled trials (RCTs) with 22,844 patients to compare bivalirudin to UFH in patients with acute myocardial infarction requiring revascularization.

Results: There was no difference between bivalirudin and UFH regarding major adverse cardiac events (MACE), risk ratio (RR) 0.99, 95% confidence interval (CI) 0.87 - 1.12; P = 0.83) or cardiovascular mortality (RR 0.87, 95% CI 0.71 - 1.07; P = 0.18). Bivalirudin increased acute stent thrombosis (RR 2.77, 95% CI 1.49 - 5.13; P = 0.001), which was only significant among ST-elevation myocardial infarction (STEMI) only trials. Bivalirudin caused less major bleeding (RR 0.66, 95% CI 0.49 - 0.90; P = 0.007), which was negated when GPI was used provisionally (RR 0.93, 95% CI 0.64 - 1.33; P = 0.67).

Conclusions: Among patients with acute myocardial infarction who underwent PCI, bivalirudin and UFH demonstrated similar MACE

and cardiovascular mortality. Bivalirudin increased acute stent thrombosis, which was more remarkable among STEMI. Bivalirudin decreased major bleeding, but this benefit was negated when GPI was used provisionally.

Introduction

In patients with acute coronary syndrome, pharmacological modulation of both the coagulation cascade and platelet activation are essential components of percutaneous coronary angiography (PCI) [1]. Unfractionated heparin (UFH) is the mainstay anticoagulant in PCI, yet it can be unreliable. The efficacy of UFH is limited by its nonspecific binding, platelet activation, variable bioactivity, and its inability to inhibit clot-bound thrombin [2]. Outside of its role in forming the fibrin clot, thrombin is a key activator of platelets, which release adenosine diphosphate (ADP) and thromboxane A2, mediators of platelet adhesion. P2Y12 binding of ADP facilitates the interaction of fibrinogen and glycoprotein IIb/IIIa, resulting in platelet aggregation and clot stabilization. Modulation of this pathway by glycoprotein IIb/IIIa inhibitors (GPI) facilitates coronary reperfusion, decreasing PCI-related reinfarction and death. Trials have demonstrated that although GPI improves the efficacy of UFH, this is at the cost of increased bleeding [3]. P2Y12 receptor antagonists are also important mediators in revascularization. Unequivocally, clopidogrel improves coronary artery patency and cardiovascular outcomes, yet its variable bioavailability and suboptimal early platelet inhibition are problematic [4, 5]. Limitations of these PCI adjuncts led to the search for more predictable therapies [2]. In 1995, a landmark study guided the approval of bivalirudin as an alternate to UFH during PCI [6]. Bivalirudin is a 20-amino-acid peptide that mimics hirudin, a naturally occurring direct thrombin inhibitor. It binds thrombin at two sites, which are interconnected by a cleavable polyglycine chain that allows simultaneous binding of fibrinogen. This unique mechanism is independent of antithrombin III, allowing for direct inhibition of both free and clot-bound thrombin. Bivalirudin demonstrates linear dose-dependent activity, resulting in more predictable pharmacokinet-

[a]Department of Cardiology, Cape Fear Valley Medical Center, Campbell University, Fayetteville, NC, USA
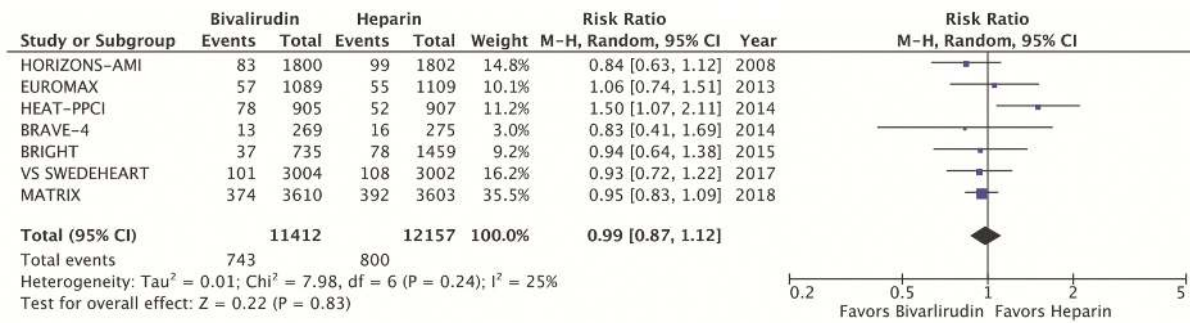[b]St Joseph's Health, New York Medical College, Paterson, NJ, USA
[c]Thomas Jefferson University Hospital, Philadelphia, PA, USA
[d]Department of Cardiology, Phoebe Putney Memorial Hospital, Albany, GA, USA
[e]Corresponding Author: Rana Garris, St Joseph's Health, New York Medical College, 703 Main St, Paterson, NJ 07503, USA.
Email: ray201603@gmail.com

Figure 1. Forest plots of meta-analysis comparing MACE between bivalirudin and heparin arms. MACEs include composite death, myocardial infarction, and stroke. MACEs: major adverse cardiac events.

ics than UFH. Bivalirudin is also associated with less bleeding, attributed to its short half-life without the risk of platelet factor-4 antibody-induced thrombocytopenia [2]. Early trials demonstrated that bivalirudin was equally efficacious with less bleeding than UFH, despite its predilection for stent thrombosis [7, 8]. While the economic benefit of bivalirudin exceeds that of UFH and routine GPI, bivalirudin costs hundreds more than UFH alone [9]. UFH monotherapy became more effective with the introduction of ticagrelor and prasugrel [10, 11]. In comparison to clopidogrel, preloading with these P2Y12 inhibitors resulted in more potent platelet inhibition, which decreased the need for routine GPI. Consequently, provisional GPI use negated the bleeding benefit of bivalirudin [12]. Two recent trials performed by modern PCI practices with potent P2Y12 inhibitors and provisional GPI resulted in similar net adverse clinical events (NACE) among bivalirudin and UFH [13, 14]. Yet, the observed overall reduction in stent thrombosis and bleeding may also be attributable to the inclusion of non-ST-elevation myocardial infarction (NSTEMI) and radial approach. The goal of this meta-analysis to assess the current role of bivalirudin in PCI.

Materials and Methods

We conducted a meta-analysis under the guidance of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) and the *Cochrane Handbook of Systemic Reviews* [15, 16]. The present study complied with the Declaration of Helsinki and was approved by the institutional review board. Electronic databases were searched for the randomized controlled trials (RCTs) that assessed bivalirudin versus UFH in patients with acute myocardial infarction who underwent PCI. We used the following individual and/or combined search terms: "bivalirudin", "unfractionated heparin", "stent", "percutaneous coronary intervention", "acute coronary syndrome", and "ST-segment elevation myocardial infarction". The search was conducted from 2000 to 2018. We identified 674 records, of which 32 duplicates were removed and 642 records screened. Of these, 619 were excluded based on title and/or abstract and 23 full text articles were reviewed for eligibility. We excluded 16 records that were conducted in predominantly (> 50%) NSTEMI, unstable angina or elective PCI. Both

STEMI and NSTEMI trials were included among patients who presented within 24 h of symptom onset with electrocardiographic changes and elevated cardiac enzymes.

We utilized Cochrane Review Manager (RevMan) 5.3 to perform this meta-analysis with the Mantel-Haenszel method to analyze dichotomous data, measuring the risk ratio (RR) with a 95% confidence interval (CI). The Cochrane Q test was used to assess heterogeneity between the trials. Heterogeneity was quantified by I-squared. A random-effects model was used for all outcomes, and subgroup analyses were performed for identifiable variances of clinical significance. Funnel plots were created to assess for publication bias, and the Cochrane GRADE tool was used to estimate the level of outcome evidence. (Supplementary Index, www.cardiologyres.org).

The primary efficacy endpoint was the incidence of MACE, which include death, myocardial infarction, and stroke at 30 days (Fig. 1). Secondary efficacy endpoints were cardiovascular mortality at 30 days (Fig. 2) and stent thrombosis with subgroup analysis of acute (< 24h) versus subacute (30 days) and STEMI versus NSTEMI (Fig. 3). Secondary safety endpoints were major bleeding at 30 days with subgroup analysis of bleeding definitions and provisional versus routine use of GPI (Fig. 4 and Supplementary Index, www.cardiologyres.org).

Results

We identified a total of seven RCT that met the inclusion criteria, yielding a total of 22,844 patients. Table 1 highlights the trial characteristics and the Supplementary Index (www.cardiologyres.org) provides more description [7, 8, 12-14, 17-19]. The primary and secondary outcomes are delineated in Figures 1 - 4. There was no difference among bivalirudin and UFH in regards to MACE (RR 0.99, 95% CI 0.87 - 1.12; P = 0.83) or cardiovascular mortality (RR 0.87, 95% CI 0.71 - 1.07; P = 0.18). There was an increased risk of acute stent thrombosis with the use of bivalirudin (RR 2.77, 95% CI 1.49 - 5.13; P = 0.001), while subacute (RR 1.15, 95% CI 0.60 - 2.21; P = 0.68) and overall (RR 1.49, 95% CI 1.00 - 2.22; P = 0.05) stent thrombosis were insignificant. In a subgroup analysis, STEMI trials appeared to have more significant stent thrombosis (RR 1.98, 95% CI 1.06 - 3.69; P = 0.03) than trials including NSTEMI (RR 1.13, 95% CI 0.70 - 1.85; P = 0.62). Bivalirudin sig-
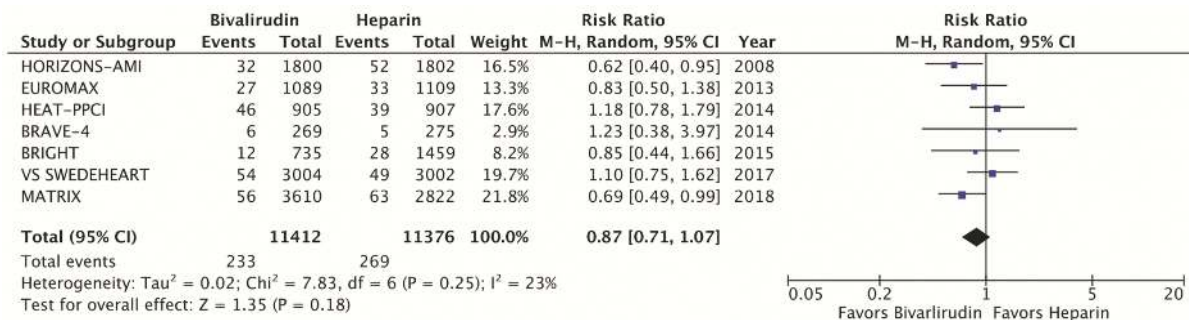
Figure 2. Forest plots of meta-analysis comparing cardiovascular mortality between bivalirudin and heparin. Cardiovascular mortality includes death due to acute myocardial infarction, pericardial tamponade, arrhythmia, peri-procedural complications or stroke.

nificantly reduced overall major bleeding as compared to UFH (RR 0.66, 95% CI 0.49 - 0.90; P = 0.007). This was negated with provisional GPI use (RR 0.93, 95% CI 0.64 - 1.33; P < 0.67) in comparison to routine (RR 0.49, 95% CI 0.37 - 0.64; P < 0.00001). Subanalysis suggested that major bleeds were more likely among trials that used the liberal HORIZONS bleeding definition [7, 8].

Discussion

This meta-analysis demonstrated that MACE and cardiovascular mortality were similar among bivalirudin and UFH, which can be explained by reinfarction and bleeding as drivers of these outcomes. HORIZONS-AMI, EUROMAX, and MATRIX showed that despite increased rates of bivalirudin stent thrombosis, bivalirudin decreased MACE and/or cardiovascular mortality [7, 19]. NACE was also decreased by bivalirudin in HORIZONS-AMI, EUROMAX, and BRIGHT [7, 18, 19]. These findings were attributable to less bleeding without an observed increase in reinfarction. Overall, only 1 trial with increased stent thrombosis displayed more reinfarction. [17]. Prior evidence established this importance, as reinfarction doubled the risk of mortality and post-PCI bleeding increased death by 5 times [20].

The low reinfarction rates observed during stent thrombosis were attributable to GPI, which was used as bailout during revascularization complicated by heavy clot burden or inadequate reflow [7, 8, 17]. Less bailout was required when there was better upstream platelet inhibition with potent P2Y12 antagonists [12, 13, 19]. The advantage of prasugrel and ticagrelor in PCI has been previously substantiated [10, 11]. BRAVE-4 showed no difference in stent thrombosis among prasugrel/bivalirudin versus clopidogrel/heparin, and required GPI bailout in only 3% of patients [12]. Ticagrelor was used in nearly all VALIDATE-SWEDEHEART patients, which demonstrated overall lower rates of stent thrombosis and reinfarction with less GPI bailout than all prior trials [13]. Moreover, its cardiovascular outcomes were independent of whether ticagrelor was given > 2 hours or < 2 hours before PCI [13]. While early optimal platelet inhibition is a clinical limitation of clopidogrel, ticagrelor achieves maximum platelet inhibition within 1 − 3 hours [5]. Rates of ischemic events

in BRAVE-4 and VALIDATE-SWEDEHEART were similar to those observed in BRIGHT with tirofiban/UFH use. Yet, while the GPI arm of BRIGHT demonstrated more bleeding, there was no significant difference among bleeding rates in BRAVE-4 and VALIDATE-SWEDEHEART [12, 13, 18]. This suggested that ticagrelor and prasugrel reduced stent thrombosis similar to GPI without the added risk of increased bleeding.

Extended infusion times of bivalirudin may have also mitigated stent thrombosis, as seen in EUROMAX, BRIGHT, and, VALIDATE-SWEDEHEART. Although all of BRIGHT patients were preloaded with clopidogrel, only 4% required bailout with similar rates of stent thrombosis and reinfarction among bivalirudin and UFH. Conversely, the MATRIX Treatment Duration study found no benefit to post-PCI bivalirudin infusion; however, this study was limited by the unspecified bivalirudin infusion regimen with variable dosing and infusion times at physician discretion [19]. A subsequent meta-analysis showed that extended bivalirudin infusion decreased cardiac events and mortality [21]. Therefore, it is reasonable to consider that the extended bivalirudin infusion regimens may have altered the rates stent thrombosis and reinfarction.

Clot burden has been considered a significant predictor of bivalirudin stent thrombosis [17]. The performed subgroup analysis demonstrated that stent thrombosis was significantly increased among STEMI trials (2.2%), but not those which included NSTEMI (1.2%). NSTEMI also had better post-PCI thrombolysis in myocardial infarction (TIMI) flow than STEMI and required less bailout GPI (Supplementary Index, www.cardiologyres.org). While more data is needed to confirm this finding, this likely had notable clinical implications.

Bivalirudin caused fewer major bleeds than UFH, which can be further analyzed in regards to bleed definition, access site, and GPI use. Earlier trials used HORIZONS, TIMI, and GUSTO bleeding definitions, while later trials used predominantly the BARC definition. The performed subgroup analysis suggested that major bleeds occurred more frequently in trials that used HORIZONS, a more liberal definition that includes access bleeds and need for blood transfusion (Supplementary Index, www.cardiologyres.org). There was no apparent difference among TIMI and GUSTO versus BARC 3 a - c and BARC 5 bleeds [22]. Radial access has been shown to reduce mortality through a reduction in bleeding [23, 24]. The MATRIX trial randomly assigned over 8,000 patients to radial or femoral ac-
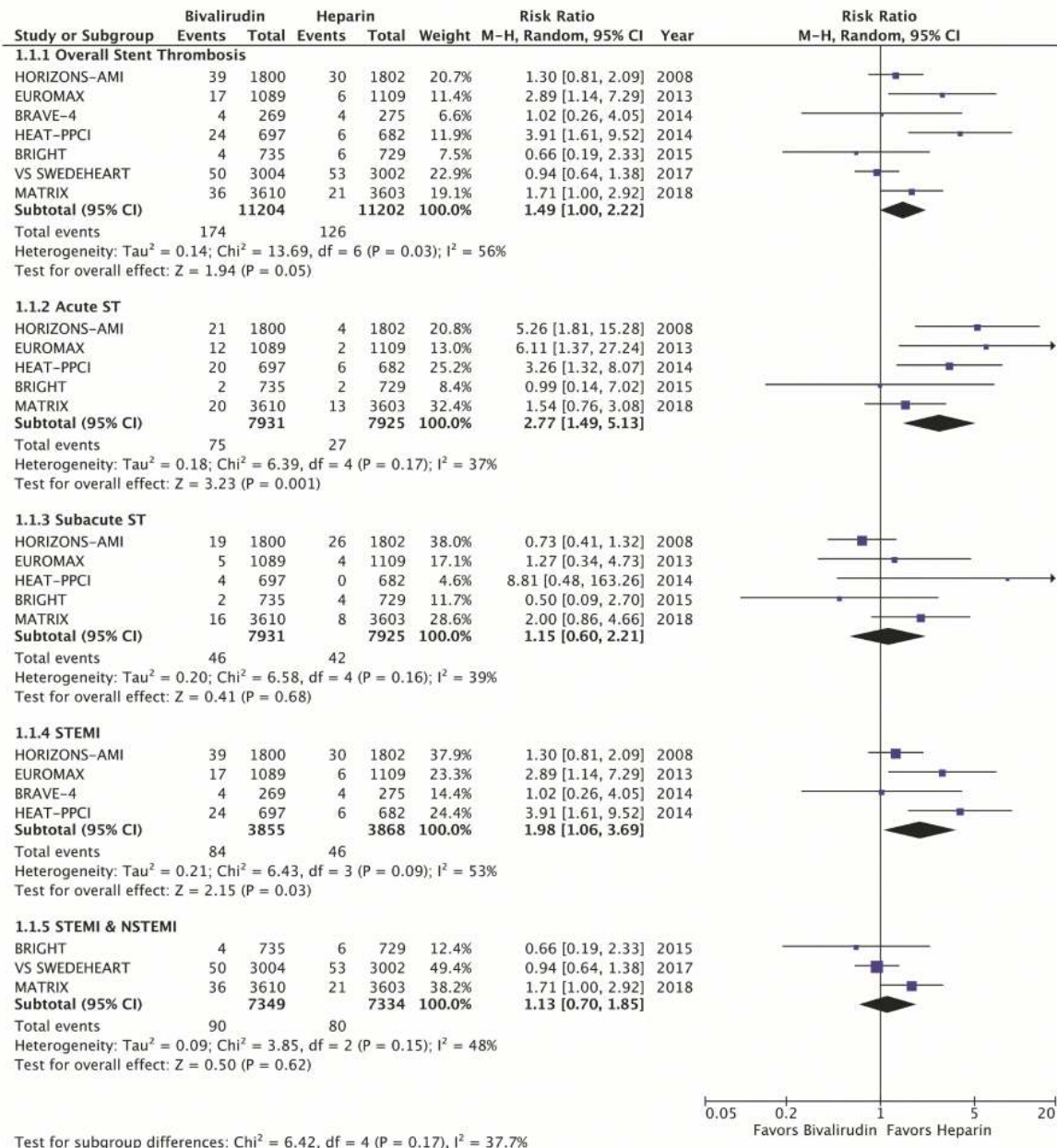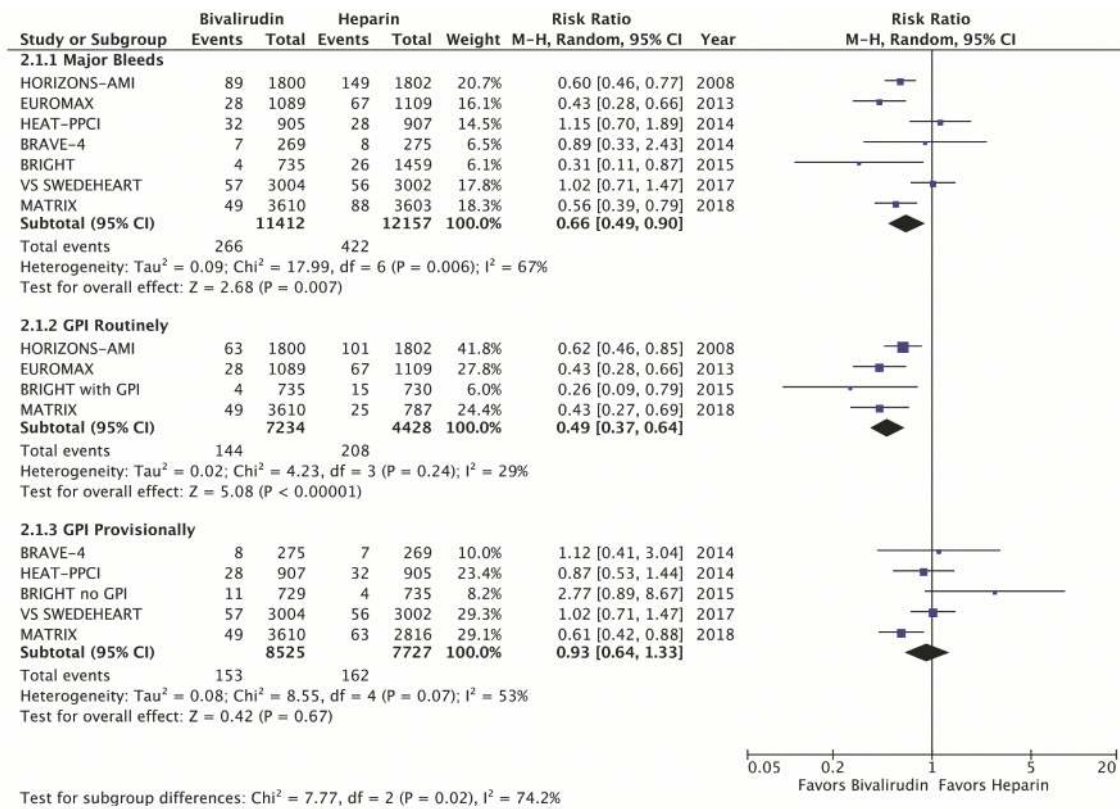
Figure 3. Forest plots of meta-analysis comparing stent thrombosis between bivalirudin and heparin. Acute stent thrombosis occurs within 24 h of PCI; subacute stent thrombosis occurs within 30 days of PCI. STEMI: ST-segment myocardial infarction; NSTEMI: non-ST segment myocardial infarction; PCI: percutaneous coronary intervention.

cess, and subsequently to bivalirudin or UFH, and showed that radial access reduced NACE and access site bleeds [14]. Trials BRIGHT, VALIDATE-SWEDEHEART, and HEAT-PPCI also predominantly used radial access [13, 17, 18]. While the bleeding benefit of bivalirudin was sustained in MATRIX and BRIGHT, it was negated in VALIDATE-SWEDEHEART and HEAT-PPCI.

GPI is potent antiplatelet therapy that improves ischemic outcomes, but it potentiates bleeding [3]. This analysis found that UFH and routine GPI resulted in significantly more major bleeds than bivalirudin (4.7% versus 2.0%). When GPI was used provisionally, this difference was insignificant (1.8% versus 2.1%). Individually, early trials with routine or discretional GPI demonstrated that bivalirudin significantly reduced bleeds [7, 8]. This was less apparent in subsequent trials where GPI was limited to bailout [12, 13, 17]. Prior studies have also demonstrated the GPI-dependent bleeding benefit of bivalirudin [25, 26]. However, the pharmacokinetics of bivalirudin may confer additional benefit [2]. This was shown in BRIGHT, where bivalirudin decreased bleeding and NACE compared to both UFH/GPI and UFH monotherapy. Similar findings were demonstrated in MATRIX, where bivalirudin reduced bleeds,

Figure 4. Forest plots of meta-analysis comparing major bleeding among bivalirudin and heparin. GPI: glycoprotein IIb/IIIa inhibitors.

notably BARC type 5, at both 30 days and 1 year. These findings were irrespective of GPI use or access site [27]. While the performed subanalysis favored bivalirudin solely in the setting of concomitant GPI, bivalirudin may be useful in patients who

Table 1. Trial Characteristics

Trial	Bivalirudin sample size	Heparin sample size	Infarction	Mean age	Radial	Pretreatment with P2Y12 inhibitors	GPI using bivalirudin	GPI using heparin
HORIZONS-AMI[a]	1,800	1,802	STEMI	60	6%	Clopidogrel	8%	98%
EUROMAX[b]	1,089	1,109	STEMI	62	46%	Clopidogrel 40%, prasugrel 33%, ticagrelor 27%	12%	69%
HEAT-PPCI[c]	905	907	STEMI	63	81%	Clopidogrel 11%, prasugrel 27%, ticagrelor 62%	13%	15%
BRAVE-4[d]	271	277	STEMI	61	1%	Prasugrel + bivalirudin, clopidogrel + UFH	3%	6%
BRIGHT[e]	735	1,459	STEMI 88%, NSTEMI 12%	58	79%	Clopidogrel	4%	6%, 100%
VALIDATE-SWEDEHEART[f]	3,004	3,002	STEMI 50%, NSTEMI 50%	68	90%	Ticagrelor 94%, prasugrel 2%, cangrelor <1%	2.5%	2.8%
MATRIX[g]	3,610	3,603	STEMI 56%, NSTEMI 44%	65	90%	Clopidogrel 46%, ticagrelor 24%, prasugrel 13%	4.6%	25.9%

[a]Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction. [b]European Ambulance Acute Coronary Syndrome Angiography. [c]How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention. [d]Bavarian Reperfusion Alternatives Evaluation. [e]Bivalirudin in Acute Myocardial Infarction vs. Heparin and GPI Plus Heparin Trial. [f]Bivalirudin versus Heparin Monotherapy in Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies Registry Trial. [g]Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox, includes Antithrombin and Treatment Duration studies.

are at greater bleeding risk.

Patient comorbidities were also important considerations. Concurrent diseases such as anemia, kidney disease, diabetes, and hypertension predispose patients to bleeding, reinfarction, and death [28, 29]. In EUROMAX, bivalirudin reduced bleeding by 3.4% when compared to UFH, yet more patients in the UFH group had anemia and chronic kidney disease (CKD). HORIZONS-AMI and EUROMAX had the highest number of patients with CKD, while subsequent trials often excluded these patients [7, 8]. BRAVE-4 showed that adverse events occurred in 20.5% of patients with diabetes, versus 14.7% in patients without diabetes [12]. Patients with diabetes also had worse outcomes in HEAT-PPCI and EUROMAX [8, 17].

There were several limitations to this meta-analysis. Clinical and methodological differences common to systematic reviews resulted in unavoidable heterogeneity. Among these were the utilized drugs and administration protocols, procedural techniques, clot burden, facility expertise, and patient baseline characteristics. UFH dose varied from 70 to 100 units/ kg and some trials allowed for pre-procedural UFH bolus in both arms. The duration and dosing regimen of bivalirudin infusion also varied, as well as the type and timing of antiplatelet therapies. Access site and bleeding definitions were both confounders, the former of which was not stratified. Clot burden was another limitation. The majority of patients had STEMI, but some trials included NSTEMI. However, all patients had acute infarction requiring revascularization. Patient comorbidities, such as CKD, diabetes, hypertension, and prior myocardial infarction also contributed to patient variability. Lastly, trials varied in their sample sizes and locations. To address these limitations, we used a random-effects model, performed subgroup analysis, and evaluated the certainty of our evidence. [15].

Conclusion

In patients with acute coronary syndrome who underwent PCI, MACE and cardiovascular mortality were similar among bivalirudin and UFH. Bivalirudin increased the risk of acute stent thrombosis, specifically among STEMI patients. Less major bleeding was observed with bivalirudin, but this was negated with provisional GPI use.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

HP, RG, SB, PS, UR and RV contributed to study design, methods, data collection and analysis, writing; GM contributed to technical methods and editing; BAG contributed to technical methods, editing and mentorship; HV, MB and FS contributed to supervising attending physicians, mentorship and guidance.

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