CLINICAL RESEARCH

CORONARY

Effect of Post–Primary Percutaneous Coronary Intervention Bivalirudin Infusion on Acute Stent Thrombosis

Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the efficacy of various doses of post–primary percutaneous coronary intervention (PCI) bivalirudin infusion to prevent acute stent thrombosis (AST).

BACKGROUND In several recent randomized controlled trials, bivalirudin infusion was continued post-PCI as either a full PCI dose (Biv-Full) or a reduced dose (Biv-Low) to reduce the risk for AST. The results of these trials varied, so the authors performed a meta-analysis of RCTs to determine whether the risk for AST is dose dependent.

METHODS Scientific databases and Web sites were searched for RCTs. A traditional meta-analysis was performed using moderator analyses and network meta-analysis using mixed-treatment comparison models to compare the efficacy of various bivalirudin doses in reducing AST.

RESULTS Data from 5 trials including 16,294 patients were analyzed. Compared with heparin, bivalirudin increased AST risk 2-fold, but this was ameliorated by continuing Biv-Full (risk ratio: 0.90, 95% confidence interval: 0.32 to 2.54; p = 0.852). This effect was not seen with Biv-Low. Similarly, in mixed-treatment models, no difference in AST rate was found between heparin and Biv-Full (odds ratio: 0.97; 95% confidence interval: 0.36 to 2.21). After 30 days, bivalirudin decreased the risk for major bleeding by 47% compared with heparin; this benefit persisted even with continued Biv-Full post-PCI (risk ratio: 0.29; 95% confidence interval: 0.16 to 0.53; p < 0.001).

CONCLUSIONS Although bivalirudin is associated with a greater risk for AST than heparin post–primary PCI, this limitation may be mitigated by continuing Biv-Full (not Biv-Low) 3 to 4 h post-operatively. The decrease in bleeding risk with bivalirudin compared with heparin is not compromised by this strategy. (J Am Coll Cardiol Intv 2016;9:1313–20) © 2016 by the American College of Cardiology Foundation.

Primary percutaneous coronary intervention (PCI) is a preferred reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI) (1). Antithrombotic therapy is essential to prevent adverse ischemic events during and after primary PCI (2). Bivalirudin and heparin are the 2 most commonly used adjunctive antithrombotic therapies during primary PCI (1,3).

A bivalirudin-based anticoagulation strategy, compared with a heparin-based strategy, decreases the risk for major bleeding at the expense of an increased risk for acute stent thrombosis (AST) (4-8). Therefore, in several recent randomized controlled trials (RCTs), bivalirudin infusion was continued post-primary PCI to ameliorate the risk for AST, but results have varied (7,9,10). However, bivalirudin doses for post-PCI infusion therapy have been variable across these trials (11). It appears that AST risk is mitigated by continuing the full dose of bivalirudin infusion post-PCI but not by low-dose infusion (9,11). To confirm this suspected trend, we performed a traditional meta-analysis using moderator analyses and a network meta-analysis using mixed-treatment comparison models to evaluate the efficacy of various doses of post-PCI bivalirudin infusion to prevent AST (12).

METHODS

STUDY DESIGN. This meta-analysis was performed according to Preferred Reporting Items for Systematic

Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses (13). A computerized review of PubMed, ClinicalTrials.gov, and the Cochrane Library databases was conducted to locate relevant studies. In addition, abstracts from major international cardiology scientific meetings were reviewed. The following keywords were used: "bivalirudin," "heparin," "stent thrombosis," "percutaneous coronary intervention," and "ST-segment elevation myocardial infarction." Trials were included if they enrolled subjects with acute STEMI undergoing primary PCI and randomly assigned patients to treatment with bivalirudin or heparin. In the case of BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial), which included both STEMI and non-STEMI patients, only STEMI subgroup data were used, but for MATRIX (Minimizing Adverse Hemorrhagic Events by Trans-radial Access Site and Systemic Implementation of Angiox) trials, overall data were included because the event rates for subgroups has not yet been reported (7,10). The BRAVE (Bavarian Reperfusion Alternatives Evaluation)-4 trial was not included in this meta-analysis, because the event rate for AST was not reported (14).

In those trials, 1 of 2 dosage rates of bivalirudin (1.75 or 0.25 mg/kg/h, termed Biv-Full and Biv-Low, respectively) was used for post-PCI infusion. Therefore, we divided patients into 3 groups: those receiving Biv-Full, those receiving Biv-Low, and those for whom bivalirudin infusion was stopped at the end of PCI, termed Biv-No. The primary efficacy endpoint was definite AST, defined as stent thrombosis within 24 h of primary PCI. The primary safety endpoint was the 30-day incidence of major bleeding, defined according to each trial. The secondary efficacy endpoint was subacute stent thrombosis, defined as stent thrombosis occurring more than 24 h, but <30 days, after primary PCI. In all included trials, an independent clinical events committee whose members were unaware of study group assignments adjudicated bleeding episodes and stent thrombosis.

STATISTICAL ANALYSIS. The traditional meta-analysis was performed according to the Comprehensive Meta-Analysis system version 3 (Biostat, Englewood, New Jersey). Pooled risk ratios (RRs) were calculated using a random-effects model. Moderator analysis was performed to examine the impact of various doses of bivalirudin post-PCI on the rate of AST. We evaluated the presence of heterogeneity across trials using the Cochran Q test and the Higgins I^2 test (15). The measure of I^2 can be

FIGURE 1 Network of Treatment Comparisons Included in the Meta-Analysis

Legend		
Drug	**Abbreviation**	**N**
Heparin	A	8304
Biv-No	B	4308
Biv-Full	C	2168
Biv-Low	D	1732

Nodes are proportional to the number of patients included in the corresponding treatments, and edges are weighted according to the number of studies included in the respective comparisons. Biv-Full = full percutaneous coronary intervention (PCI) dose (1.75 mg/kg/h) bivalirudin for post-PCI infusion; Biv-Low = reduced dose (0.25 mg/kg/h) bivalirudin for post-PCI infusion; Biv-No = no post-PCI bivalirudin infusion.
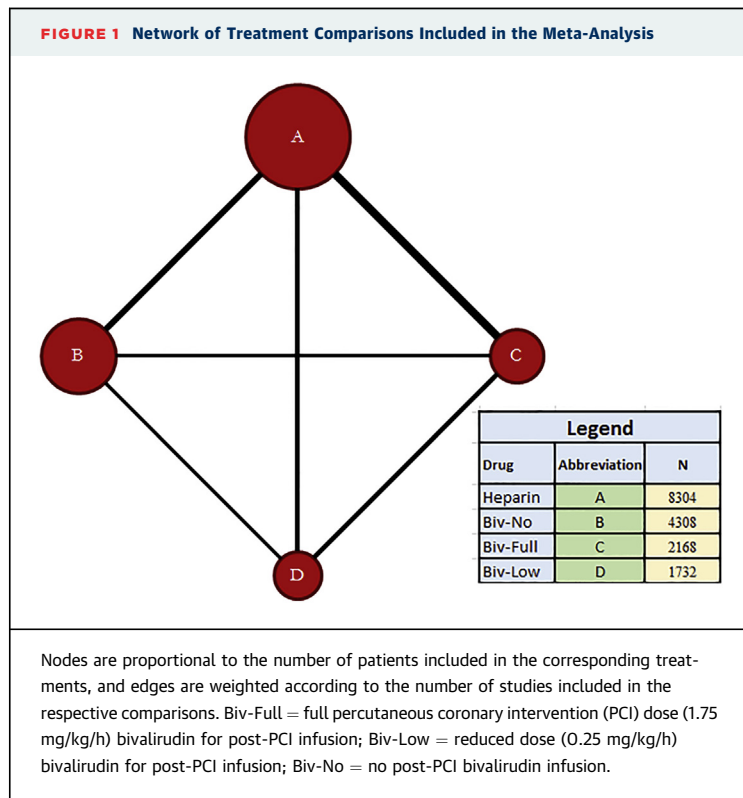
TABLE 1 Characteristics of Included Trials

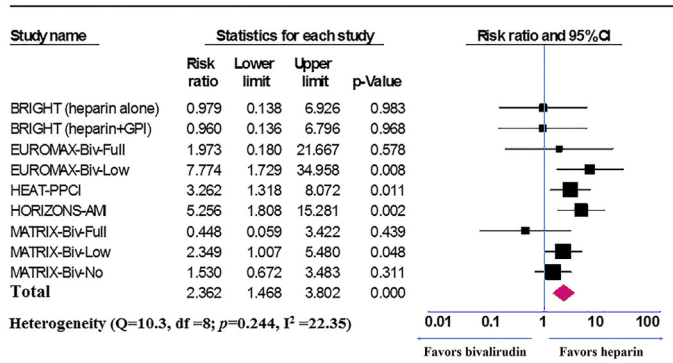| Study Name (Ref. #)	Bivalirudin Arm (n)	Heparin Arm (n)	GPIs (%) Bivalirudin Arm	GPIs (%) Heparin Arm	P2Y$_{12}$ Inhibitors*
BRIGHT (heparin alone) (7)	655	641	4.6	5.6	Clopidogrel 100%
BRIGHT (heparin + GPI) (7)	655	629	4.6	100.0	Clopidogrel 99.9%
EUROMAX, Biv-Full (9)	670	947	11.5†	69.1	Clopidogrel 50%† Prasugrel 30.8% Ticagrelor 19.2%
EUROMAX, Biv-Low (9)	244	947	11.5†	69.1	Clopidogrel 50%† Prasugrel 30.8% Ticagrelor 19.2%
HEAT-PPCI (19)	905	907	13.0	15.0	Clopidogrel 12.1% Prasugrel 27% Ticagrelor 61%
HORIZONS-AMI (4)	1,800	1,802	7.2	94.5	Clopidogrel 99.2% Ticlopidine 0.4%
MATRIX, Biv-Full (10)	618	3,603	3.6†	25.9	Clopidogrel 53.9%† Prasugrel 20.2% Ticagrelor 35.1%
MATRIX, Biv-Low (10)	1,062	3,603	3.6†	25.9	Clopidogrel 53.9%† Prasugrel 20.2% Ticagrelor 35.1%
MATRIX, Biv-No (10)	1,811	3,603	5.5	25.9	Clopidogrel 53.7% Prasugrel 22.7% Ticagrelor 34.6%

*Calculated as the sum of P2Y$_{12}$ platelet inhibitor use at admission and at the catheterization laboratory for the bivalirudin arm. †Data for overall bivalirudin post-PCI infusion group. Study investigators did not report data for the bivalirudin subgroups (Biv-Full and Biv-Low).

Biv-Full = full PCI dose (1.75 mg/kg/h) bivalirudin for post-PCI infusion; Biv-Low = reduced dose (0.25 mg/kg/h) bivalirudin for post-PCI infusion; Biv-No = no post-PCI bivalirudin infusion; BRIGHT = Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial; EUROMAX = European Ambulance Acute Coronary Syndrome Angiography Trial; GPI = glycoprotein IIb/IIIa inhibitor; HEAT-PPCI = How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; MATRIX = Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox.

FIGURE 2 Acute Stent Thrombosis
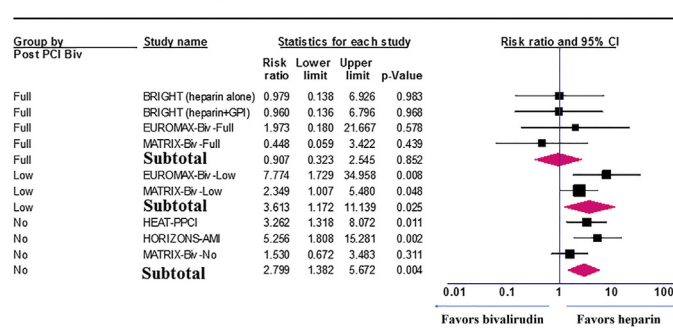
(A) Individual and pooled risk ratios for acute stent thrombosis. **(B)** Forest plots with moderators' analyses showing the impact of various doses of post-percutaneous coronary intervention (PCI) bivalirudin infusion on the risk for acute stent thrombosis. The risk ratio estimate of each study is marked with a **square**. The **size of the square** represents the weight that the corresponding study exerts in the meta-analysis. The larger the **square**, the greater the study contribution to the overall estimate. **Diamond** indicates overall summary estimate for the analysis (**width of the diamond** represents the 95% confidence interval). Trial acronyms as in **Table 1**.

interpreted as the percentage of variability resulting from heterogeneity between studies, rather than the sampling error (15). When heterogeneity was discovered, sensitivity analysis was performed, where 1 study at a time was excluded, and the impact on the summary results of removing each was evaluated (16). Publication bias was not assessed, because the number of included trials was inadequate (<10) to properly assess a funnel plot or to use more advanced regression-based assessments (17).

Bayesian network meta-analysis was performed using random-effects models because it is the most conservative methodology to account for between-trial heterogeneity (12). All analyses were performed using WinBUGs Bayesian software package and Net-MetaXL (Cornerstone Research Group, Burlington, Ontario, Canada) (18). We estimated the relative ranking probability of each treatment and obtained the treatment hierarchy of competing interventions using a league table and surface under the cumulative ranking curve (18). Inconsistency was assessed by

FIGURE 3 Acute Stent Thrombosis

The network meta-analysis comparison of various doses of post–percutaneous coronary intervention (PCI) bivalirudin infusion with each other and with heparin for the acute stent thrombosis. Biv-Full = full PCI dose (1.75 mg/kg/h) bivalirudin for post-PCI infusion; Biv-Low = reduced dose (0.25 mg/kg/h) bivalirudin for post-PCI infusion; Biv-No = no post-PCI bivalirudin infusion; CI = confidence interval; OR = odds ratio. *Sample size for the combined groups for each comparison.

comparing the deviance residuals and deviance information criterion statistics in fitted consistency and inconsistency models (18).

RESULTS

BASELINE CHARACTERISTICS. Five RCTs met criteria for inclusion, involving 16,294 patients. Our search flow diagram is shown in Online Figure 1. The network of treatment comparisons is shown in **Figure 1**. **Table 1** describes the characteristics of the individual trials. In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) trials, bivalirudin infusion was stopped at the end of PCI (4,19). In the BRIGHT trial (per mandated protocol), all patients in the bivalirudin arm received Biv-Full for a median duration of 3 h (7). The EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) protocol specified that the bivalirudin infusion should be continued for 4 h after PCI at the Biv-Low dose. However, the option to continue the infusion at the full dose for up to 4 h was also allowed (5). Thus, 73% received Biv-Low and 27% received Biv-Full post-PCI. In the MATRIX trial, patients were randomly assigned

at a 1:1 ratio to receive bivalirudin or heparin. Patients who were assigned to the bivalirudin group were subsequently randomly assigned at a 1:1 ratio to receive a post-PCI bivalirudin infusion or no post-PCI infusion. The MATRIX investigators let individual practitioners choose the bivalirudin dose for post-PCI infusion (either Biv-Full for up to 4 h or Biv-Low for at least 6 h), which led to the majority of practitioners' using reduced doses. Thus, 63% of the patients received Biv-Low and 37% received Biv-Full post-PCI.

CLINICAL OUTCOMES. In the direct comparison meta-analysis, bivalirudin use increased the risk for AST compared with heparin (RR: 2.36; 95% confidence interval [CI]: 1.46 to 3.02; p < 0.001), but this risk was completely ameliorated by continuing Biv-Full (RR: 0.90; 95% CI: 0.32 to 2.54; p = 0.852) (**Figure 2**). This effect was not seen with Biv-Low (RR: 3.61; 95% CI: 1.17 to 11.13; p = 0.025) or Biv-No (RR: 2.79; 95% CI: 1.38 to 5.67; p = 0.004). There was no significant heterogeneity among the trials (Q = 10.3, df = 8, p = 0.244, I^2 = 22.35). Bivalirudin use was not associated with an increased risk for subacute stent thrombosis (RR: 1.14; 95% CI: 0.53 to 2.42; p = 0.731) compared with heparin (Online Figure 2).

Similarly, in the mixed-treatment comparison models, no difference in AST rate was found between
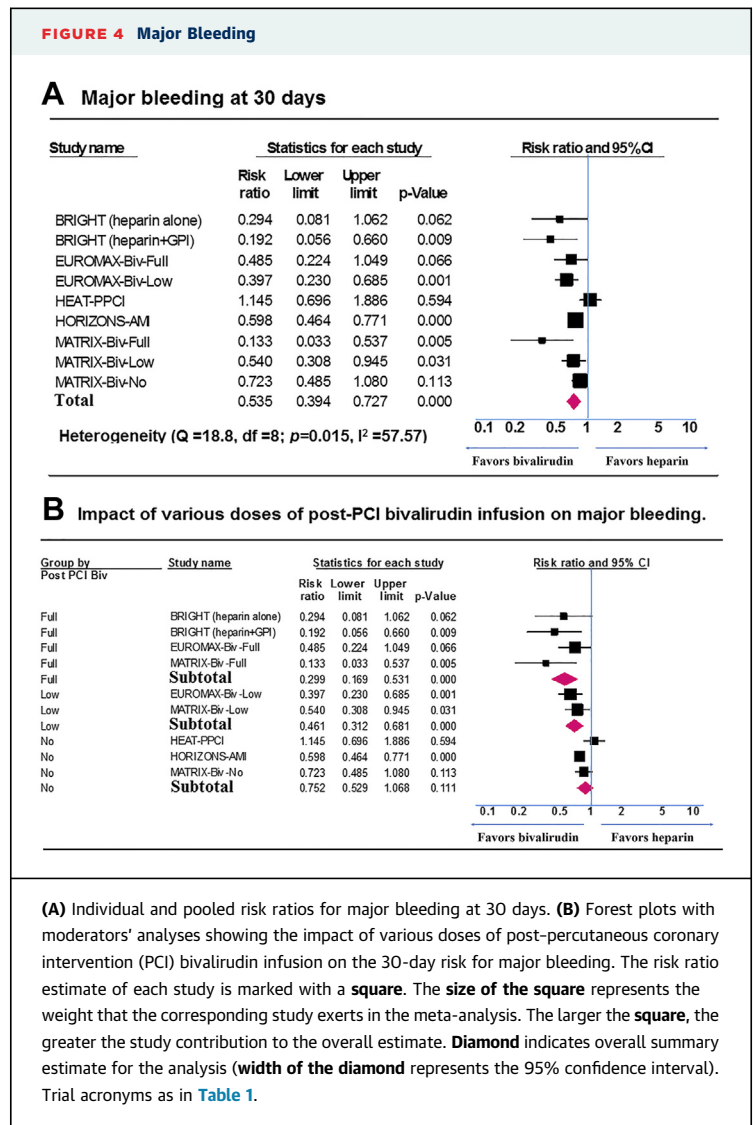
heparin and Biv-Full (odds ratio [OR]: 0.97; 95% CI: 0.36 to 2.21), but the rate of AST among those receiving heparin was lower compared with those receiving Biv-Low (OR: 0.25; 95% CI: 0.12 to 0.57) or Biv-No (OR: 0.33; 95% CI: 0.17 to 0.56) (Figure 3). At treatment ranking, Biv-Full ranked as the best therapy, followed closely by heparin (Online Figure 3). On the basis of the surface under the cumulative ranking curve values derived from trials included in our network meta-analysis, Biv-Full had an 83% probability of being ranked as the best therapy for AST prevention, while the probability for heparin was 82%. The probabilities for Biv-No and Biv-Low were 25% and 8%, respectively. We did not detect inconsistency among the trials.

In the direct comparison meta-analysis, bivalirudin decreased the risk for major bleeding at 30 days compared with heparin (RR: 0.53; 95% CI: 0.39 to 0.72; p < 0.001); this benefit persisted with continued Biv-Full use post-PCI (RR: 0.29; 95% CI: 0.16 to 0.53; p < 0.001) (Figure 4). There was significant between-trial heterogeneity for major bleeding (Q = 18.8, df = 8, p = 0.015, I^2 = 57.57). During sensitivity analysis, once the single-center trial (HEAT-PPCI) was removed, there was no significant heterogeneity (Q = 11.3, df = 7, p = 0.123, I^2 = 38.46) among the 4 remaining (multicenter) trials (Online Figure 3) (20). Thus, heterogeneity seemed to originate from the single-center study (HEAT-PPCI). Similarly, during sensitivity analyses, removing HEAT-PPCI changed the summary results for moderator's analyses by showing that all 3 bivalirudin groups experienced less risk for major bleeding compared with heparin (Online Figure 4).

The mixed-treatment comparison models yielded results similar to those found using direct comparison models: those receiving Biv-Full retained a lower rate of major bleeding at 30 days compared with those receiving heparin (OR: 0.26; 95% CI: 0.14 to 0.46) (Figure 5).
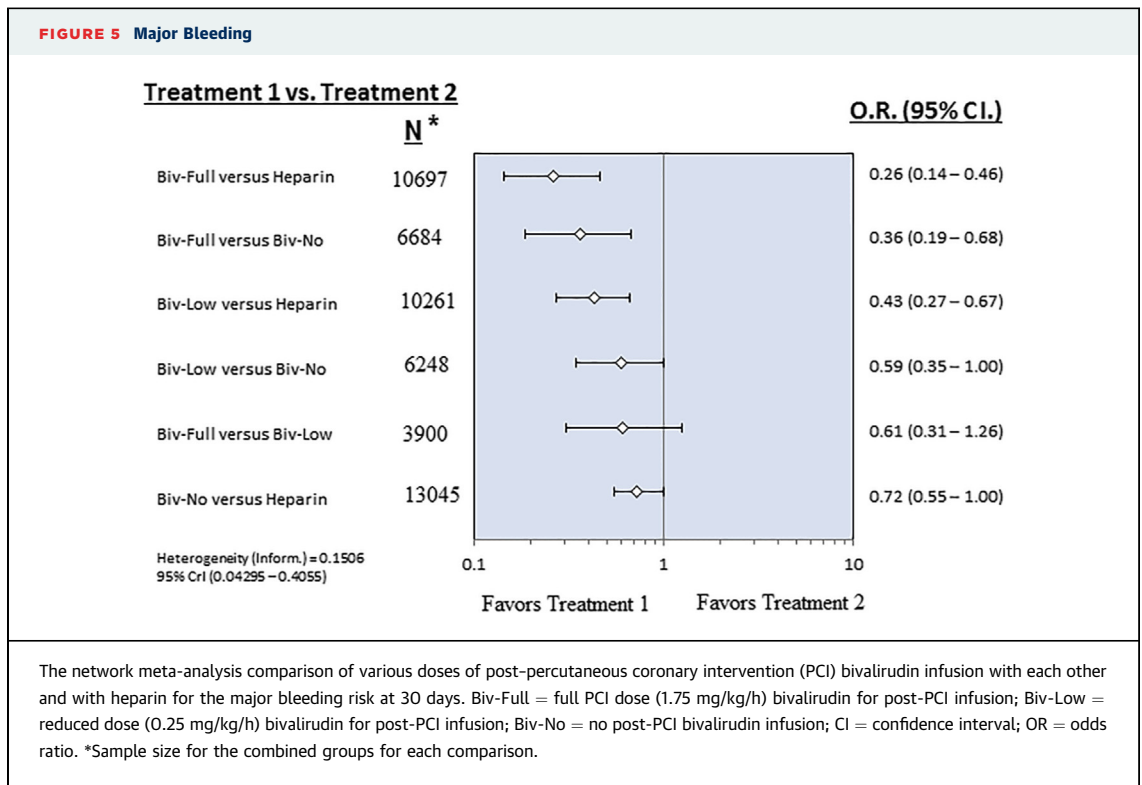
DISCUSSION

In this study of 16,294 patients enrolled in 5 RCTs, we compared the effect of bivalirudin-based anti-coagulation therapy during primary PCI with a heparin-based regimen on AST and major bleeding. A bivalirudin-based regimen significantly decreased the 30-day risk for major bleeding by 47% at the expense of a 2-fold increased risk for AST. However, the increased risk for AST may be mitigated by continuing Biv-Full for 3 to 4 h postoperatively, but not if the Biv-Low dose was used. Furthermore, the decreased bleeding risk with bivalirudin compared

FIGURE 4 Major Bleeding

A Major bleeding at 30 days

Study name	Risk ratio	Lower limit	Upper limit	p-Value
BRIGHT (heparin alone)	0.294	0.081	1.062	0.062
BRIGHT (heparin+GPI)	0.192	0.056	0.660	0.009
EUROMAX-Biv-Full	0.485	0.224	1.049	0.066
EUROMAX-Biv-Low	0.397	0.230	0.685	0.001
HEAT-PPCI	1.145	0.696	1.886	0.594
HORIZONS-AMI	0.598	0.464	0.771	0.000
MATRIX-Biv-Full	0.133	0.033	0.537	0.005
MATRIX-Biv-Low	0.540	0.308	0.945	0.031
MATRIX-Biv-No	0.723	0.485	1.080	0.113
Total	**0.535**	**0.394**	**0.727**	**0.000**

Heterogeneity (Q =18.8, df =8; p=0.015, I^2 =57.57)

Favors bivalirudin   Favors heparin

B Impact of various doses of post-PCI bivalirudin infusion on major bleeding.

Group by Post PCI Biv	Study name	Risk ratio	Lower limit	Upper limit	p-Value
Full	BRIGHT (heparin alone)	0.294	0.081	1.062	0.062
Full	BRIGHT (heparin+GPI)	0.192	0.056	0.660	0.009
Full	EUROMAX-Biv-Full	0.485	0.224	1.049	0.066
Full	MATRIX-Biv-Full	0.133	0.033	0.537	0.005
Full	**Subtotal**	**0.299**	**0.169**	**0.531**	**0.000**
Low	EUROMAX-Biv-Low	0.397	0.230	0.685	0.001
Low	MATRIX-Biv-Low	0.540	0.308	0.945	0.031
Low	**Subtotal**	**0.461**	**0.312**	**0.681**	**0.000**
No	HEAT-PPCI	1.145	0.696	1.886	0.594
No	HORIZONS-AMI	0.598	0.464	0.771	0.000
No	MATRIX-Biv-No	0.723	0.485	1.080	0.113
No	**Subtotal**	**0.752**	**0.529**	**1.068**	**0.111**

Favors bivalirudin   Favors heparin

(A) Individual and pooled risk ratios for major bleeding at 30 days. (B) Forest plots with moderators' analyses showing the impact of various doses of post-percutaneous coronary intervention (PCI) bivalirudin infusion on the 30-day risk for major bleeding. The risk ratio estimate of each study is marked with a **square**. The **size of the square** represents the weight that the corresponding study exerts in the meta-analysis. The larger the **square**, the greater the study contribution to the overall estimate. **Diamond** indicates overall summary estimate for the analysis (**width of the diamond** represents the 95% confidence interval). Trial acronyms as in **Table 1**.

with heparin does not appear to be attenuated by continuing Biv-Full infusion for 3 to 4 h post-intervention.

Primary PCI is the standard of care for patients with STEMI (1,3). STEMI is a heightened state of inflammation and thrombosis, and PCI can further increase the risk for acute intracoronary thrombosis by disrupting the coronary endothelium, leading to vessel closure during or soon after the procedure (2). Therefore, all international guidelines recommend adjunctive antithrombotic treatment with anticoagulant and antiplatelet agents for primary PCI (1,3). However, antithrombotic agents can also cause bleeding, which is strongly associated with early and late mortality (21,22). Thus, balancing the anti-ischemic benefits against the bleeding risk of these agents is of paramount importance in assessing new

FIGURE 5 Major Bleeding

The network meta-analysis comparison of various doses of post-percutaneous coronary intervention (PCI) bivalirudin infusion with each other and with heparin for the major bleeding risk at 30 days. Biv-Full = full PCI dose (1.75 mg/kg/h) bivalirudin for post-PCI infusion; Biv-Low = reduced dose (0.25 mg/kg/h) bivalirudin for post-PCI infusion; Biv-No = no post-PCI bivalirudin infusion; CI = confidence interval; OR = odds ratio. *Sample size for the combined groups for each comparison.

therapies and managing patients with STEMI (23). In several RCTs and meta-analyses, bivalirudin-based regimens have been shown to significantly decrease the risk for major bleeding, but AST remained a serious problem with bivalirudin (4,8).

Bivalirudin has a short half-life (25 min), and therefore, thrombin activity is restored fairly rapidly when the infusion stops (24). This creates a vulnerable period for stent thrombosis arising from a gap between the waning antithrombin effect of bivalirudin and the onset of platelet inhibition from oral $P2Y_{12}$ inhibitors (25,26). This vulnerable period for AST was confirmed by the EUROMAX investigators. In their study, ASTs were clustered in the first few hours after primary PCI, occurring at a median of just 2.3 h (interquartile range: 1.9 to 2.8 h) from the start of angiography (9). To have an antithrombotic agent on board during this vulnerable period, BRIGHT investigators continued Biv-Full post-procedure with a median duration of 3 h, which completely attenuated the risk for AST (7). Similarly, the EUROMAX investigators showed in a post hoc analysis that the risk for AST can be abated by the continued use of a post-procedural Biv-Full infusion, but not by Biv-Low (9). In MATRIX, members of the bivalirudin group were randomly assigned in a 1:1 ratio to receive a post-PCI bivalirudin infusion or no post-PCI infusion (10). A post-PCI bivalirudin infusion

did not decrease the AST risk in the overall post-PCI bivalirudin arm of the MATRIX trial. The MATRIX investigators let individual practitioners choose bivalirudin doses for post-PCI infusion, which led to the majority of practitioners' using Biv-Low, possibly explaining the lack of benefit. However, even the MATRIX study suggested a dose-response phenomenon. The incidence of definite stent thrombosis among patients receiving Biv-Full was lower than among those receiving Biv-Low (0.2% vs. 2.1%). Furthermore, the incidence of definite stent thrombosis in the heparin arm was higher than in the Biv-Full arm (0.6% vs. 0.2%). Indeed, the MATRIX investigators pointed out this issue as one of their study limitations.

To our knowledge, this is the first meta-analysis to address the effect of prolonging post-PCI bivalirudin infusion on AST and major bleeding by using traditional and network meta-analyses. Our findings suggest that 3 to 4 h post-procedure, a Biv-Full (1.75 mg/kg/h bivalirudin) infusion may mitigate the risk for AST without increasing the risk for major bleeding. Paradoxically, in our analyses, Biv-No was not associated with decreased risk for bleeding compared with heparin. However, in a random model, the relative weight from the HEAT-PPCI for the Biv-No group was 25%. Given the single-center nature of the HEAT-PPCI trial, it is possible that its findings

reflect an exaggerated therapeutic effect relative to a multicenter trial (20,27). Prior analyses have suggested that the HEAT-PPCI trial may be a major outlier in this regard (8,28). Therefore, in our sensitivity analysis, excluding HEAT-PPCI made all 3 bivalirudin groups significantly more effective in decreasing the bleeding risk compared with heparin (Online Figure 4).

STUDY LIMITATIONS. First, in the majority of these trials, the patients were not randomized to receive or not receive a post-procedure PCI bivalirudin infusion. Thus, we cannot state with certainty whether post-procedure Biv-Full infusion was responsible for the lower rates of AST risk. Therefore, our findings should be interpreted cautiously. Additional RCTs are needed to confirm these findings.

Second, we did not have individual participant data, and thus the data were combined from various studies. Each study had its own protocol and definitions. In particular, the type of P2Y$_{12}$ platelet inhibitor used and the use of glycoprotein IIb/IIIa inhibitors was variable across the studies. These could have cofounded our findings. Access to patient-level data would enable multivariate analysis and markedly strengthen this analysis. In addition, the MATRIX investigators have not reported event rates for subgroups, so we had to include overall MATRIX data (combining STEMI and non-STEMI patients). However, during the sensitivity analyses, removal of the MATRIX trial data did not affect the summary results (Online Figure 5).

Finally, not all trials reported probable stent thrombosis rates for bivalirudin subgroups, so our analyses were limited to definite stent thrombosis only.

CONCLUSIONS

In primary PCI, bivalirudin significantly decreases the 30-day risk for major bleeding at the expense of an increased risk for AST compared with heparin. However, the increased risk for AST may be mitigated by continuing a full PCI dose of bivalirudin 3 to 4 h post-PCI. The decreased bleeding risk with bivalirudin, compared with heparin, is not compromised by this strategy.

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PERSPECTIVES

WHAT IS KNOWN? A bivalirudin-based anticoagulation regimen during primary PCI significantly decreases risk for major bleeding at the expense of an increased risk for AST.

WHAT IS NEW? A 3- to 4-h post-procedure bivalirudin infusion at full PCI dose (1.75 mg/kg/h) may mitigate the risk for AST without increasing the risk for major bleeding.

WHAT IS NEXT? Further RCTs are needed to evaluate the impact of a post–primary PCI bivalirudin infusion on AST, cardiovascular mortality and all-cause mortality.

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APPENDIX For supplemental figures, please see the online version of this article.