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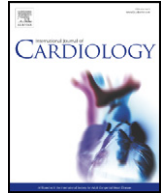
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Comparison of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing an invasive strategy: A meta-analysis of randomized clinical trials

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ABSTRACT

Objective: This meta-analysis was performed to assess the efficacy and safety of bivalirudin compared with unfractionated heparin or enoxaparin plus glycoprotein (GP) IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention (PCI).

Background: Pharmacotherapy for patients undergoing PCI includes bivalirudin, heparin, and GP IIb/IIIa inhibitors. We sought to compare ischemic and bleeding outcomes with bivalirudin versus heparin plus GP IIb/IIIa inhibitors in patients undergoing PCI.

Methods: A literature search was conducted to identify fully published randomized trials that compared bivalirudin with heparin plus GP IIb/IIIa inhibitors in patients undergoing PCI.

Results: A total of 19,772 patients in 5 clinical trials were included in the analysis (9785 patients received bivalirudin and 9987 patients received heparin plus GP IIb/IIIa inhibitors during PCI). Anticoagulation with bivalirudin, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, results in no difference in major adverse cardiovascular events (odds ratio [OR] 1.07, 95% confidence interval [CI] 0.96 to 1.19), death (OR 0.93, 95% CI 0.72 to 1.21), or urgent revascularization (OR 1.06, 95% CI 0.86 to 1.30). There is a trend towards a higher risk of myocardial infarction (OR 1.12, 95% CI 0.99 to 1.28) but a significantly lower risk of TIMI major bleeding with bivalirudin (OR 0.55, 95% CI 0.44 to 0.69).

Conclusion: In patients who undergo PCI, anticoagulation with bivalirudin as compared with unfractionated heparin or enoxaparin plus GP IIb/IIIa inhibitors results in similar ischemic adverse events but a reduction in major bleeding.

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In conjunction with contemporary pharmacologic therapy, percutaneous coronary intervention (PCI) results in excellent clinical outcomes in patients with coronary artery disease. However, adverse events associated with PCI include periprocedural ischemic events,

recurrent revascularization and bleeding [1]. Unfractionated heparin was the traditional antithrombin agent used during PCI to prevent ischemic complications [2]. The administration of glycoprotein (GP) IIb/IIIa inhibitors in addition to heparin results in additional reduction of periprocedural ischemic events but also increases the risk of bleeding complications [3,4]. Recent data have shown that bleeding complications at the time of PCI have been associated with higher mortality after PCI [5–7]. This has resulted in continued investigation into alternative pharmacologic agents for optimal ischemic efficacy during PCI while decreasing hemorrhagic complications.

The direct thrombin inhibitor, bivalirudin (Angiomax, the Medicines Company, Fort Lee, NJ), a synthetic polypeptide derived from the native anticoagulant hirudin, is an attractive alternative to heparin in patients who undergo PCI [8]. Randomized clinical trials comparing bivalirudin with heparin plus GP IIb/IIIa inhibitors in patients who undergo PCI demonstrated that bivalirudin had comparable rates of ischemic complications with lower rates of major bleeding compared

Abbreviations: ACT, activated clotting time; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; CACHET, Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial; GP, glycoprotein; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; PCI, percutaneous coronary intervention; PROTECT-TIMI-30, Randomized Trial to Evaluate the Relative PROTECTION against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents—Thrombolysis in Myocardial Infarction-30; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; TIMI, Thrombolysis in Myocardial Infarction.

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to heparin plus GP IIb/IIIa [9–13]. However, several of these studies were noninferiority trials and not designed to demonstrate a difference in clinical events [9–11]. Two prior meta-analyses have been performed to date comparing these anticoagulants in PCI that support the efficacy of bivalirudin in PCI [14,15]. However, both studies did not include the ACUITY and HORIZONS-AMI trials of high-risk PCI patients. Therefore, we conducted a meta-analysis of all published, prospective randomized trials to evaluate the efficacy and safety of bivalirudin monotherapy with GP IIb/IIIa inhibitors used in a provisional fashion compared with heparin plus GP IIb/IIIa inhibitors.

1. Methods

1.1. Literature review

We conducted a computerized literature review of MEDLINE, EMBASE and Cochrane databases from 2000 to 2009 for randomized clinical trials using keywords “heparin”, “glycoprotein IIb/IIIa inhibitor”, “bivalirudin”, and “percutaneous coronary intervention.” We also used Science Citation Index to cross-reference for studies that met our criteria.

1.2. Selection criteria

The studies included in the meta-analysis were based on predetermined criteria which were (1) prospective randomized clinical trials, (2) published as manuscripts in peer-reviewed journals with full available text in English, (3) compared the use of unfractionated heparin or enoxaparin plus GP IIb/IIIa inhibition versus bivalirudin with the provisional use of glycoprotein IIb/IIIa inhibitors in patients undergoing PCI, and (4) length of follow-up of at least 48 hours after PCI.

1.3. Endpoints/data abstraction

The primary endpoint was major adverse cardiovascular events, which was defined as the composite of death, myocardial infarction, and repeat revascularization. The secondary endpoints were death, myocardial infarction, repeat revascularization, and major bleeding. Repeat revascularization was performed either according to study protocol or due to a clinical indication. The TIMI major criterion for bleeding, which is bleeding associated with >5 g/dL decrease in hemoglobin or $>15\%$ absolute decrease in hematocrit, intracranial bleed, or cardiac tamponade, was used. Three independent reviewers (M.S.L., T.Y., and J.D.) extracted the following data: the first author of the study, baseline demographics, sample size, clinical events (death, myocardial infarction, repeat revascularization, stent thrombosis, and bleeding), and length of follow-up.

1.4. Statistical analysis

The meta-analysis was done using the Comprehensive Meta-Analysis (CMA) system version 2. For each study included in this analysis, odds ratios (OR) as well as confidence intervals (CI) were calculated based on the rates comparing the use of heparin and glycoprotein IIb/IIIa inhibitor together against the use of bivalirudin. A fixed model of meta-analysis was used to aggregate the study level data. To assess heterogeneity among studies for each outcome, the Cochran's Q statistic was computed. The associated p-value of chi-square test for the presence of heterogeneity was presented. The overall baseline characteristics were calculated using weighted means and standard deviations for continuous variables and weighted proportions for binary variables. The p-values for comparing the two group baseline covariates using a two-sample t-test for continuous data and chi-square test for categorical data were performed with Microsoft Excel as ancillary software. All the p-values were 2-tailed with statistical significance level at 0.05, and CI was calculated to 95%.

2. Results

2.1. Baseline characteristics

Five randomized controlled studies met our criteria for inclusion in the meta-analysis (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events-2 [REPLACE-2], Acute Catheterization and Urgent Intervention Triage Strategy [ACUITY], Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI], Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial [CACHET], and Randomized Trial to Evaluate the Relative PROTECTION against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents—Thrombolysis in Myocardial Infarction-30 [PROTECT-TIMI-30] trials)

(Table 1) [9–13]. A total of 19,772 patients were included in the analysis (9785 patients received bivalirudin and 9987 patients received heparin plus GP IIb/IIIa inhibitors during PCI). Clinical follow-up ranged from 48 h (PROTECT-TIMI-30), 7 days (CACHET), to 30 days (REPLACE-2, ACUITY, and HORIZONS-AMI) after PCI. All study protocols recommended a loading dose of clopidogrel before PCI except for the ACUITY trial in which the administration of clopidogrel was left to the discretion of the investigators. Dual anti-platelet therapy was continued for a minimum of 30 days to 6 months depending on the protocol of the study.

In the REPLACE-2 and CACHET trials, patients undergoing elective PCI were included while acute myocardial infarction patients were excluded. The ACUITY and PROTECT-TIMI-30 trials included patients with non-ST-elevation acute coronary syndromes, and the HORIZONS-AMI trial included patients with ST-elevation myocardial infarction. In all the studies in this meta-analysis, patients assigned to the bivalirudin group also received provisional glycoprotein IIb/IIIa inhibitors for predetermined criteria such as coronary artery dissection and thrombus formation. Rates of such provisional GP IIb/IIIa inhibitor administration ranged from 7.2% in the REPLACE-2 trial to 24% in CACHET.

2.2. Clinical outcomes

Patients who received bivalirudin, as compared with patients who received heparin plus GP IIb/IIIa inhibitors, had similar rates of major adverse cardiovascular events (OR 1.07, 95% CI 0.96 to 1.19) (Fig. 1). There was no significant heterogeneity among the studies ($p = 0.46$).

The mortality rate for the bivalirudin group was 1.2% and in the heparin with glycoprotein IIb/IIIa inhibitor group, the mortality rate was 1.3% (OR 0.93, 95% CI 0.72 to 1.21) (Fig. 2). The CACHET trial was not included in the analysis as there were no deaths in either group at a follow-up of 7 days. The p-value of testing for heterogeneity among studies was on the borderline ($p = 0.05$).

There was a trend towards a higher risk of myocardial infarction with bivalirudin as compared with heparin plus GP IIb/IIIa inhibitors (OR 1.12, 95% CI 0.99 to 1.28) (Fig. 3). The 30-day myocardial infarction rate did not include CACHET because follow-up was up to 7 days and 30-day event rates were not reported. There was no significant heterogeneity among the studies ($p = 0.96$).

The rate of urgent revascularization was 2.0% in the bivalirudin group and 1.9% in the heparin with glycoprotein IIb/IIIa inhibitor group (OR 1.06, 95% CI 0.86 to 1.30) (Fig. 4). The urgent revascularization rate does not include the PROTECT-TIMI-30 trial because event rates were not reported. There was no significant heterogeneity among the studies ($p = 0.36$).

The risk of TIMI major bleeding was lower with bivalirudin as compared with heparin plus GP IIb/IIIa inhibitors (OR 0.55, 95% CI 0.44 to 0.69) (Fig. 5). This was not unexpected since all 5 trials reported either a trend towards less bleeding or significantly lower rates associated with bivalirudin. There was no significant heterogeneity among the studies ($p = 0.70$).

3. Discussion

The primary finding in this meta-analysis is that anticoagulation with bivalirudin compared to heparin and GP IIb/IIIa inhibitors results in equivalent rates of major adverse cardiovascular events, death, and urgent revascularization in patients who undergo PCI. There was a trend towards a higher risk of myocardial infarction with bivalirudin compared with heparin plus GP IIb/IIIa inhibitors. However, the use of bivalirudin is associated with a significantly reduced rate of TIMI major bleeding compared to heparin plus GP IIb/IIIa inhibitors. Despite evidence that bleeding events are independently associated with higher one-year mortality rates after PCI [5–7], the reduction in TIMI major bleeding in the bivalirudin group did not result in a short-term reduction in mortality.

Table 1
Summary of clinical trials.

Trial	Type of patients	Number of patients enrolled	Length of follow-up	Bivalirudin doses	Heparin dose	ACT target in the heparin/GP IIb/IIIa group (s)	Provisional GP IIb/IIIa use in bivalirudin group (%)	Primary endpoint	Secondary endpoints
CACHET [13]	Elective PCI	268	7 days	0.5 mg/kg or 0.75 mg/kg bolus with 1.75 mg/kg/h infusion	70 U/kg bolus	No pre-specified target	24	Composite death, MI, or revascularization ^a ; major bleeding; maximum hemoglobin drop by 7 days or discharge.	None
PROTECT-TIMI-30 [12]	Unstable angina or NSTEMI	857	48 h	0.75 mg/kg bolus with 1.75 mg/kg/h infusion	50 U/kg bolus; 0.5 mg/kg enoxaparin	200–250	Not published	Coronary flow reserve and TIMI major bleeding during PCI.	Peak troponin after PCI; Holter monitor ischemia; composite death, MI, or Holter monitor ischemia at 48 h.
REPLACE-2 [10]	Elective stenting, unstable angina	6010	30 days	0.75 mg/kg bolus with 1.75 mg/kg/h infusion	65 U/kg bolus; 0.5 mg/kg enoxaparin	225	7.2	Composite death, MI, revascularization, major bleeding at 30 days.	Death; MI; revascularization; major bleeding; minor bleeding at 30 days.
ACUITY [11]	Unstable angina or NSTEMI	13,819	30 days	0.5 mg/kg bolus with 1.75 mg/kg/h infusion	60 U/kg bolus; 1 mg/kg enoxaparin	200–250	9.1	Composite death, MI, revascularization; major bleeding at 30 days.	Death, MI, revascularization, major bleeding at 30 days.
HORIZONS-AMI [9]	STEMI	3602	30 days	0.75 mg/kg bolus with 1.75 mg/kg/h infusion	60 U/kg bolus	200–250	7.2	Major bleeding; composite major bleeding, death, MI, revascularization, and stroke at 30 days.	Major bleeding; death; MI; revascularization; stroke; stent thrombosis.
Age (years) (%)	Male (%)	Hypertension (%)	Smoking (%)	Prior PCI (%)	Prior CABG (%)	Congestive heart failure (%)	Prior stroke (%)		
65/62 NA	73/77	NA	NA	NA	NA	NA	NA		
60/60 NA	68/66	66/66	44/37	36/38	24/25	7/7	6/5		
63/63 NA	75/74	66/68	28/26	27/26	35/35	18/19	7/7		
63/63 NA	69/71	57/57	28/28	29/29	40/39	18/18	NA		
60/61 NA	77/76	52/55	16/17	47/45	11/11	3/3	NA		

Data are presented as bivalirudin/heparin/GP IIb/IIIa inhibitor.

ACT – activated clotting time; ACUITY – Acute Catheterization and Urgent Intervention Triage Strategy trial; CABG – coronary artery bypass graft surgery; CACHET – Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial; GP – glycoprotein; HORIZONS-AMI – Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction study; MI – myocardial infarction; NA – not available; NSTEMI – non-ST-elevation myocardial infarction; PCI – percutaneous coronary intervention; PROTECT-TIMI-30 – Randomized Trial to Evaluate the Relative PROTECTION against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents–Thrombolysis in Myocardial Infarction-30; REPLACE-2 – Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events trial; STEMI – ST-elevation myocardial infarction; and TIMI – Thrombolysis in Myocardial Infarction.

^a Urgent unplanned revascularization of target vessel by percutaneous coronary intervention or surgery.

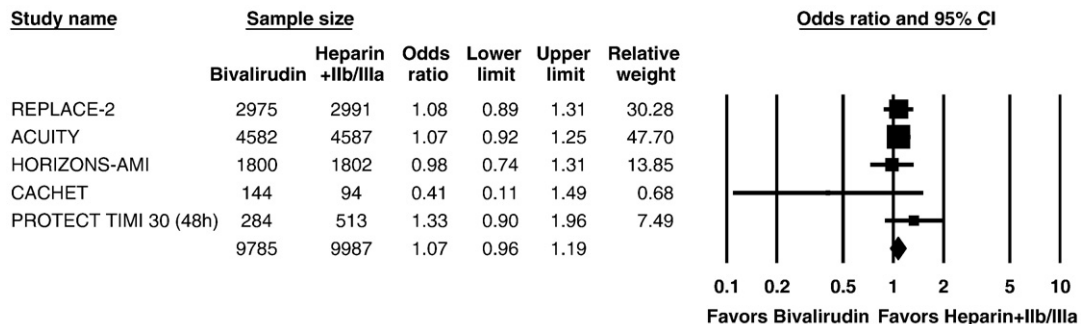


Fig. 1. The odds ratio and summary plots for major adverse cardiovascular events.

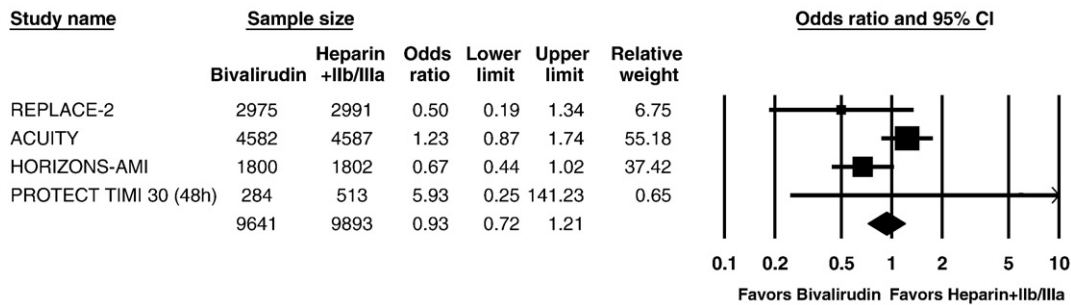


Fig. 2. The odds ratio and summary plots for mortality.

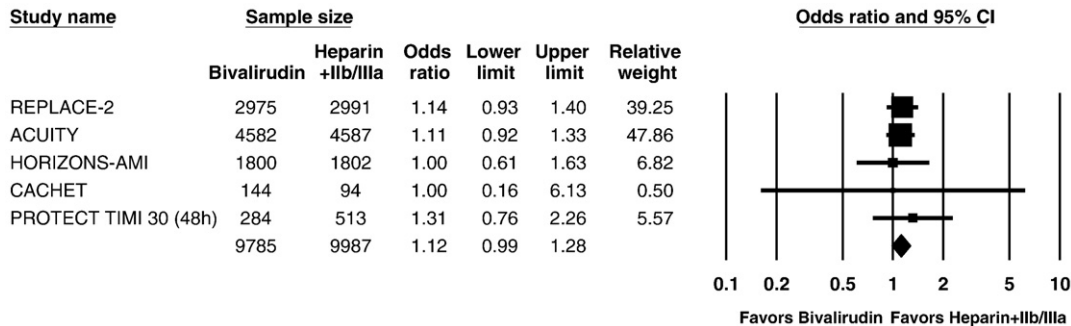


Fig. 3. The odds ratio and summary plots for myocardial infarction.

In general, meta-analyses allow for evaluation of individual trial results with greater statistical power so that smaller differences in outcomes may be identified. The REPLACE-2, ACUITY, and HORIZONS-AMI trials were only powered to demonstrate noninferiority of bivalirudin to heparin plus GP IIb/IIIa inhibitors leading to a concern that small differences in ischemic endpoints were not being detected [16,17]. Likewise, the PROTECT-TIMI-30 and CACHET trials were underpowered for clinical endpoints [12,13]. Despite the increased power afforded by combining the results of the above trials in this meta-analysis, no statistically significant differences in major adverse cardiovascular events and mortality endpoints were found. These findings support the utility of bivalirudin in PCI with similar ischemic efficacy but a superior safety profile in reducing hemorrhagic complications.

The association between myocardial infarction during PCI and impaired long-term (≥ 1 year) survival has been reported [18,19]. Despite a trend towards a higher risk of myocardial infarction with bivalirudin compared with heparin plus GP IIb/IIIa inhibitors observed in this analysis, no detectable difference in short-term mortality was observed.

In spite of the lower bleeding with bivalirudin, no mortality benefit was observed in this analysis. However, the HORIZONS-AMI trial reported a reduction in 30-day mortality in patients presenting with ST-elevation myocardial infarction who underwent PCI with bivalirudin compared with heparin and GP IIb/IIIa inhibitors. One-year outcomes in

the HORIZONS-AMI trial continued to show that bivalirudin is associated with a lower rate of major bleeding (15.6% versus 18.3%, $p < 0.0001$) and mortality (3.5% versus 4.8%, $p = 0.037$) [20]. Furthermore, the mortality benefit reported in the HORIZONS-AMI trial could be attributed to the fact that the study population which included patients with ST-elevation myocardial infarction had a higher mortality rate and that the differences in the mortality rates were, thus, more easily identifiable. However, one-year outcomes in the ACUITY trial did not show a statistically significant difference in the 2 treatment groups which included more patients and is consistent with the results of this meta-analysis [21].

The survival advantage in such patients who received bivalirudin could potentially be explained by a reduction in the risk of bleeding, need for transfusion, need for vasopressors in patients who develop hypotension, discontinuation of anti-platelet therapy which may lead to stent thrombosis, and thrombocytopenia. The mechanism of reduced bleeding events with bivalirudin could be due to its predictable pharmacokinetics and its lack of effect on platelet activation. Bivalirudin results in a dose-dependent prolongation of activated partial thromboplastin time, prothrombin time, and thrombin time. Concurrent aspirin administration does not change the pharmacokinetics of this drug and has no effect on template bleeding times [8]. Also, it is cleared by both the kidneys and by intravascular proteolysis, making its pharmacokinetics less susceptible to renal dysfunction [22].

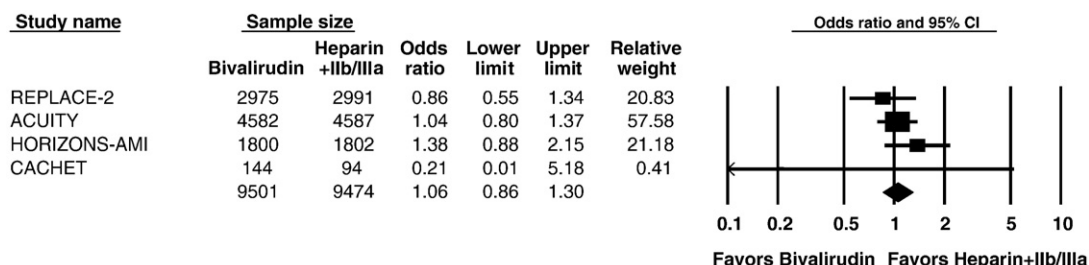


Fig. 4. The odds ratio and summary plots for repeat revascularization.



Fig. 5. The odds ratio and summary plots for major bleeding.

3.1. Limitations

This study utilized summarized published event rates for each trial as opposed to individual patient data. Access to individual patient data would have enabled further subgroup analyses to address this question. In the ACUITY and HORIZONS-AMI trials, there was a large fraction of patients (approximately two thirds) in the bivalirudin treatment arms in each of these trials that received unfractionated heparin or enoxaparin prior to randomization, possibly confounding the results [9,11,17]. Patients who received GP IIb/IIIa inhibitors were pooled into one group, regardless of whether they received unfractionated heparin or enoxaparin. The impact of different GP IIb/IIIa inhibitors on the clinical outcomes is unknown.

Data extracted from randomized trials may not reflect the patients seen in “real-world” practice. Only five prospective randomized trials fit into the inclusion criteria for this meta-analysis which makes this study prone to publication bias. The clinical trials included in this meta-analysis included patients along the full spectrum of coronary artery disease from patients undergoing elective PCI to those being treated with primary PCI for acute myocardial infarction. Patients received varying doses of unfractionated heparin. Higher doses of heparin resulting in greater activated clotting times have been associated with an increased risk of bleeding [23]. The dosing, timing, and administration rate of thienopyridines varied in the clinical trials. Pretreatment with thienopyridines in patients who receive bivalirudin may play an important role in platelet inhibition and provide similar protection from ischemic events compared with heparin plus GP IIb/IIIa inhibitors. In the ACUITY trial, patients who were not treated with thienopyridines prior to angiography or PCI and received bivalirudin had a higher risk of composite ischemic events compared with patients treated with heparin plus GP IIb/IIIa inhibitors [11].

Although one-year outcomes were available for the HORIZONS-AMI and ACUITY trials, 30-day outcomes were used because the other studies in this meta-analysis had similar duration of follow-up [20,21]. Using the one-year outcomes may have affected the mortality rate because the survival curves in the HORIZONS-AMI trial continued to diverge after 30 days [20].

In conclusion, this meta-analysis shows with significantly greater statistical power that anticoagulation with bivalirudin during PCI is equivalent to unfractionated heparin or enoxaparin plus GPIIb/IIIa inhibitors with respect to ischemic major adverse cardiovascular events but is associated with a significantly lower rate of major bleeding.

Conflict of interest

Michael S. Lee: Speaker's Bureau—Schering-Plough, BSCI, BMS, Daiichi-Sankyo.
 Jonathan Tobis: Speaker's Bureau—BSCI.
 Tae Yang: None.
 Ehtisham Mahmud: Research grants for clinical trials: Boston Scientific, Abbott Vascular.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [24].

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