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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.

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 morality 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.