What are the Factors that Could Contribute to the Lower Risk of Major Bleeding with Bivalirudin Compared with Unfractionated Heparin for Percutaneous Coronary Intervention?

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The benefit of bivalirudin in reduction of major bleeding compared with unfractionated heparin in percutaneous coronary intervention remains a matter of ongoing debate. Multiple meta-analyses had illustrated a substantial reduction in the risk of major bleeding with bivalirudin [1,2,3]. However, we noted a significant degree of heterogeneity in the outcome of major bleeding in such meta-analyses [1,2,3]. Meanwhile, in a recently published meta-analysis comparing both agents through a radial approach there was no difference in the risk of major bleeding, with a moderate degree of heterogeneity (I²=44%) [4]. In that meta-analysis, the authors noted potential effect modification between glycoprotein IIb/IIIa inhibitors administration, and the dose of unfractionated heparin used in the control arm with the risk of major bleeding [4]. Therefore, we aimed to test for such effect on a larger scale and to explore whether those factors could explain the heterogeneity observed in previous meta-analyses.

An electronic search of electronic databases was conducted from inception until April 2016 for randomized clinical trials that compared bivalirudin with unfractionated heparin in percutaneous coronary intervention for any indication, using the keywords: “bivalirudin”, “hirulog”, “angiomax”, “heparin”, “bleeding”, “percutaneous coronary intervention” and “mortality”. Both authors independently extracted the data regarding the outcome of major bleeding from the included trials. The primary outcome was major bleeding, as identified by each trial. Random effects risk ratios were calculated using DerSimonian and Laird method for the overall outcome of major bleeding. A pre-specified subgroup analysis was conducted for major bleeding according to the method of glycoprotein IIb/IIIa administration in each trial (i.e., planned or bailout). A pre-specified meta-regression analysis was conducted for all the included trials for the outcome of major bleeding with the dose of unfractionated heparin in the control arm. If a trial reported an unfractionated heparin dose range, we used the upper limit of the range as the regression variable. Two similar regression analyses were conducted for trials reporting balanced glycoprotein IIb/IIIa inhibitors use in both arms and for those with planned glycoprotein IIb/IIIa inhibitors use in the unfractionated heparin arm only. The overall meta-regression was conducted with a presumed confidence interval (CI) of 95% and p-value <0.05 for statistical significance.

A total of 20 trials were included in the final analysis. The incidence of major bleeding was 3.2% in the bivalirudin arm compared to 4.6% in the unfractionated heparin arm (RR 0.65, 95% CI 0.54-0.79, p<0.0001, I²=63%). On subgroup analysis by the method of glycoprotein IIb/IIIa inhibitors use in each trial, the incidence of major bleeding was significantly lower in trials using planned glycoprotein IIb/IIIa inhibitors in the unfractionated heparin arm only (RR 0.55, 95% CI 0.49-0.62, p<0.0001, I²=0%) but not in trials using planned or bailout glycoprotein IIb/IIIa inhibitors in a balanced fashion in both arms (RR 1.08, 95% CI 0.89-1.30, p=0.09, I²=23%; and RR 0.8, 95% CI 0.62-1.03, p=0.45, I²=0%; respectively), Pinteraction <0.0001 (Figure 1).

The overall meta-regression for major bleeding with the unfractionated heparin dose in the control arms for all trials was not statistically significant (p=0.6). The same observation

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was noted when planned glycoprotein IIb/IIIa inhibitors use was limited to the unfractionated heparin arm only (p=0.46). However, the meta-regression was significant when the use of glycoprotein IIb/IIIa inhibitors was balanced in both arms (i.e. either planned or bail-out in both arms) (p=0.012) (Figure 2).

The findings of this meta-regression analysis of randomized trials illustrated the crucial effect of the method of glycoprotein IIb/IIIa inhibitors administration and the dose of unfractionated heparin on the risk of major bleeding observed with unfractionated heparin compared with bivalirudin for PCI. Although bivalirudin significantly decreased the incidence of major bleeding for PCI for any indication compared with unfractionated heparin, such effect was obvious when planned glycoprotein IIb/IIIa inhibitors were used in the unfractionated heparin arm only and was not observed with balanced glycoprotein IIb/IIIa inhibitors use in both arms. The benefit was also noted only with higher doses of unfractionated heparin only, when the influence of glycoprotein IIb/IIIa inhibitors was balanced in both arms. Such results are similar to previous studies that explored the effect of bivalirudin versus unfractionated heparin on major bleeding, when the analysis was limited only to trials reporting balanced glycoprotein IIb/IIIa inhibitors use in both groups [5].

The planned use of glycoprotein IIb/IIIa inhibitors in PCI has been shown by multiple studies to be associated with a higher risk of major bleeding and questionable added benefit in the era of potent adenosine di-phosphate (ADP) antagonists [6,7]. As a result, a shift occurred in the trend of administration of these agents from an upstream planned approach to a rather downstream bailout approach, with the planned approach limited only to special situations, such as inadequate ADP antagonists loading or patients with high risk of thrombosis [8]. The current study confirmed that planned glycoprotein IIb/IIIa inhibitors could confound the comparison between bivalirudin with unfractionated heparin in PCI [9]. Therefore, the unequal use of glycoprotein IIb/IIIa inhibitors between both arms might have resulted in an apparent superiority of bivalirudin over unfractionated heparin in reducing the risk of major bleeding.

In conclusion, both the method of glycoprotein IIb/IIIa administration and the dose of unfractionated heparin influence the major bleeding benefit observed bivalirudin in patients undergoing PCI. The benefits of bivalirudin were obvious only when planned glycoprotein IIb/IIIa inhibitors were used in the unfractionated heparin arm only, and with higher doses of unfractionated heparin when bailout glycoprotein IIb/IIIa inhibitors were used in both arms.

**Declarations of Interest**
The authors declare no conflicts of interest.

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The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [10].

**References**

