

## VIEWPOINTS

# Is Heparin an Acceptable Anticoagulant When Glycoprotein IIb/IIIa Inhibitors Are Not Used?



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The relationship between bleeding complications and increased mortality after percutaneous coronary intervention (PCI) has been well documented. Bivalirudin is superior to heparin and glycoprotein (GP) IIb/IIIa inhibitors, mainly due to the lower risk of bleeding but comparable rates of ischemic complications (1-3). Three trials presented at the 2014 American College of Cardiology Scientific Sessions raise questions regarding the superiority of bivalirudin in PCI (4-6).

In the HEAT-PPCI (Unfractionated Heparin Versus Bivalirudin in Primary Percutaneous Coronary Intervention) trial, 1,829 patients from a single center with ST-segment elevation myocardial infarction (STEMI) referred for primary PCI were randomized to heparin (70 U/kg bolus) or bivalirudin, with GP IIb/IIIa inhibitor only used for bail out (15.5% vs. 13.5%,  $p = \text{NS}$ ) (4). The majority of the PCI (>80%) were performed transradially. Nearly all patients (99.6%) were preloaded with dual antiplatelet therapy; 60% of patients received ticagrelor and 27% received prasugrel. The primary efficacy endpoint of major adverse cardiac events at 4 weeks, defined as all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularization, was lower in the heparin group (5.7% vs. 8.7%; relative risk [RR]: 1.52, 95% confidence interval [CI]: 1.1 to 2.1,  $p = 0.01$ ), which was driven by less reinfarction and target lesion revascularization without any increase in bleeding complications (3.1% vs. 3.5%,  $p = 0.59$ ). Definite or probable stent thrombosis was also lower

(0.9% vs. 3.4%; RR: 3.91, 95% CI: 1.6 to 9.5,  $p = 0.001$ ), whereas mortality was similar (4.3% vs. 5.1%,  $p = \text{NS}$ ). Ethical concerns were raised as informed consent was obtained after PCI in those who survived.

In the BRAVE (Bavarian Reperfusion Alternatives Evaluation)-4 trial, 548 patients with ST-segment elevation myocardial infarction who underwent transfemoral PCI (except for 1 patient) were randomized to either: 1) a prasugrel 60-mg loading dose plus bivalirudin; or 2) heparin (70- to 100-IU/kg bolus) plus a clopidogrel 600-mg loading dose (5). Bailout GP IIb/IIIa inhibitors were used in 3% of the prasugrel/bivalirudin group and 6% of the clopidogrel/heparin group. Unfortunately, the trial was terminated early due to slow recruitment, which, therefore, limits our ability to make definitive conclusions. The primary composite endpoint of all-cause death, recurrent myocardial infarction, unplanned revascularization of the infarct-related artery, definite stent thrombosis, stroke, or major bleeding at 30 days was similar in the prasugrel/bivalirudin group compared with the clopidogrel/heparin group, as was non-coronary artery bypass grafting-related bleeding and mortality.

In the NAPLES (Novel Approaches in Preventing or Limiting Events) III trial, 837 patients undergoing elective transfemoral (99.5%) PCI deemed to be at high risk for bleeding complications were randomized to bivalirudin or heparin (70 U/kg bolus followed by 20 U/kg to maintain an activated clotting time above 250 s) (6). The primary endpoint of in-hospital major

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bleeding was similar between the bivalirudin and heparin groups. At 30 days, clinical endpoints were also similar: major adverse cardiac events, death, myocardial infarction, stent thrombosis, and major bleeding. Bailout use of GP IIb/IIIa inhibitor was uncommon in both groups.

Previous studies suggested a possible increased risk of ischemic complications with bivalirudin. In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stent in Acute Myocardial Infarction) trial, patients treated with bivalirudin had an increased risk of acute stent thrombosis (1.3% vs. 0.3%,  $p < 0.001$ ). The 1-year mortality rate was lower in patients treated with bivalirudin compared with heparin and GP IIb/IIIa inhibitor (3.5% vs. 4.8%,  $p = 0.037$ ), which might possibly be explained by the increased bleeding rate with GP IIb/IIIa inhibitors (3). In the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, patients treated with bivalirudin that were not pre-treated with dual antiplatelet therapy had increased ischemic complications compared with those treated with heparin and GP IIb/IIIa inhibitor (9.1% vs. 7.1%, RR: 1.29, 95% CI: 1.03 to 1.63) (2).

In elective PCI, the REPLACE (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical

Events)-2 trial demonstrated that bivalirudin was not inferior to heparin and GP IIb/IIIa inhibitors in terms of suppression of acute ischemic endpoints but was associated with less bleeding (1). However, the use of GP IIb/IIIa inhibitors is rare in elective PCI.

Assessing the safety and efficacy of anticoagulation on such a dynamic landscape is clearly a challenge. Three recent trials suggest that, when a GP IIb/IIIa inhibitor is selectively used, heparin, if dosed appropriately, is a cost-effective antithrombotic agent for PCI when patients are pre-loaded with dual antiplatelet therapy, with significant cost savings. The higher risk of bleeding observed in the previous trials may be attributed to high doses of heparin and the use of GP IIb/IIIa inhibitors, although its current use is infrequent and limited to a small, high-risk group with heavy thrombotic burden. Further studies are needed to determine the optimal antithrombotic and antiplatelet regimens that provide the least bleeding and ischemic complications.

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