

The Role of Bivalirudin in Percutaneous Coronary Intervention

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Bivalirudin (angiomax) is a reversible direct thrombin inhibitor. It is a polypeptide that has a carboxy-terminal region that recognizes thrombin's fibrinogen-binding site, and an amino-terminal tetrapeptide that inhibits the active site of thrombin. It is considered superior to its prototype; hirudin as it is less dependent on renal function and has a lower incidence of anaphylaxis. Bivalirudin has a half-life of 25 minutes and is primarily eliminated via proteolytic cleavage. Compared to heparin, direct thrombin inhibitors, such as bivalirudin, exhibit less variable level of anticoagulation, and they inactivate both free as well as fibrin-bound thrombin. [1]

In most cardiac catheterization laboratories across the United States, Bivalirudin is used mainly as a heparin substitute such as in patients intolerant to heparin (e.g. history of HIT syndrome). However, Bivalirudin clinical studies have demonstrated consistent positive outcomes in patients with stable angina, unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI). This therapy has also gained class I recommendation from the ACC/AHA updated guidelines for all of the above mentioned conditions. [2, 3]

The *Bivalirudin Angioplasty Trial* (BAT) was a randomized, double-blinded, multi-center trial that included 4098 patients undergoing PCI for unstable angina. In this trial, the composite endpoint of death, MI or revascularization was lower in the bivalirudin arm at 90 days with absolute benefits being sustained through 180 days. There was also a significant reduction in the rate of bleeding in the bivalirudin arm compared to heparin. [4]

Similarly, the *Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events* (REPLACE)-1 trial evaluated the efficacy of bivalirudin relative to heparin in patients undergoing PCI. Glycoprotein (GP) IIB/IIIA inhibitors were used in 72 % of patient and clopidogrel was used in 56% of patients. The incidence of composite end point of death, myocardial infarction, or repeat revascularization was not significantly different between the bivalirudin and heparin groups (5.6% and 6.9% respectively, $p = 0.40$). Major bleeding occurred in 2.1% versus 2.7% of patients randomized to bivalirudin or heparin, respectively ($p = 0.52$). [5]

In the *Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events* (REPLACE)-2 trial, patients were assigned to either bivalirudin, with provisional use of GP IIB/IIIA inhibitor or low-dose unfractionated heparin (UFH) plus planned GP IIB/IIIA inhibitor. There was similar rate of 30-day primary composite endpoint of death, MI, urgent revascularization, and in-hospital major bleeding between the bivalirudin and the heparin-GP IIB/IIIA groups. [6] However, bivalirudin led to significantly less in-hospital major bleeding when compared to the heparin-GP IIB/IIIA inhibitor combination (2.4% versus 4.1%, $p < 0.001$). There was a difference in mortality favoring bivalirudin at 30 days and 6 months, and 12 months.

Higher risk patients with UA/NSTEMI who were considered for an early invasive strategy were evaluated in the *Bivalirudin for Patients with Acute Coronary Syndromes* (Acuity Trial). In this pivotal trial, 13,819 patients were assigned to one of three anti-thrombotic regimens: unfractionated heparin or enoxaparin plus a glycoprotein IIB/IIIA inhibitor, bivalirudin plus a glycoprotein IIB/IIIA inhibitor, or bivalirudin alone. The rates of 30 day ischemic outcomes were similar between bivalirudin plus GP IIB/IIIA inhibitor compared with heparin

plus GP IIB/IIIA inhibitor (7.7% and 7.3%, respectively). There were also similar rates of major bleeding (5.3% and 5.7%). As compared with heparin plus GP IIB/IIIA inhibitor, bivalirudin, alone, led to noninferior rates of ischemia (7.8% and 7.3%, respectively; $P=0.32$), and significantly reduced major bleeding (3.0% vs. 5.7%; $P<0.001$). [7]

Bivalirudin also underwent evaluation in the setting of STEMI patients. In the *Bivalirudin during Primary PCI in Acute Myocardial Infarction* (HORIZONS-AMI trial) [8]. This was a multicenter trial that enrolled 3602 patients with ST-segment elevation myocardial infarction who were undergoing primary PCI. The patients were randomized to a regimen of heparin plus a GP IIB/IIIA inhibitor versus bivalirudin alone. Treatment with bivalirudin alone, as compared with heparin plus GP IIB/IIIA inhibitors was associated with a significant reduction in the 30-day primary endpoint of net adverse clinical events which was predominantly driven by a lower rate of major bleeding. It also lowered 30-day rates of death from cardiac causes (1.8% vs. 2.9% $P=0.03$) as well as death from all causes (2.1% vs. 3.1% $P=0.047$). Follow up at one, two, and three years showed that the reduction in the incidence of net adverse clinical events and major bleeding was robustly maintained in the bivalirudin monotherapy group. [8]

Conclusion

Bivalirudin represents an attractive option as an antithrombotic agent in the cardiac catheterization laboratory. It has several advantages over heparin, and based upon evidence from many clinical trials, it has been proven to be safer than and at least as effective as heparin in the STEMI, NSTEMI/UA, and elective PCI population. We expect that the use of this agent as an antithrombotic therapy during PCI will continue to gain traction in the next few years.

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