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EDITORIAL COMMENT

Heparin May Be Hard to Beat

However Much You Are Willing to Spend on Bivalirudin*

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There is now general agreement, based on research from the last 20 years, that the use of bivalirudin—rather than heparin—confers no advantage in terms of reduced ischemic events (1,2). Indeed, an increased rate of acute stent thrombosis (and the associated sequelae of myocardial infarction and unplanned revascularization) has been a consistent finding with bivalirudin treatment, particularly in the recent trials examining primary percutaneous coronary intervention (PCI) (3–5).

Our recent trial, HEAT-PPCI (Unfractionated Heparin Versus Bivalirudin in Primary Percutaneous Coronary Intervention) (4), recruited a near "all-comers" population, and the observed adverse event rates more closely matched institutional norms and the results reported by national registries (e.g., 1-month mortality: HEAT-PPCI 4.7%, HORIZONS-AMI 2.6%). The relative risk of acute stent thrombosis (AST) was less dramatic in HEAT-PPCI (3.26; 95% confidence interval [CI]: 1.32 to 8.07) than in HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) (5.19; 95% CI: 1.79 to 15.08) or EUROMAX (European Ambulance Acute Coronary Syndrome Angiography Trial) (6.11; 95% CI: 1.37 to 27.74), but the study may give a good estimate of current, "real-world," absolute AST event rates for a strategy of procedural monotherapy with bailout glycoprotein IIb/IIIa inhibitor (GPI) use (and in the absence of systematic use of heparin in the bivalirudin arm).

Bivalirudin has a loyal cadre of enthusiastic users. The drug has attractive features, including a well-established procedural dose regime, a predictable biological effect, no need for monitoring with tests of clotting function, and a short half-life. Use of bivalirudin rather than heparin in higher doses (100 to 140 U/kg body weight) will almost certainly reduce bleeding complications. Because of this, there will be great interest in the description of a strategy to reduce or abolish the hazard of AST.

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In this issue of *JACC: Cardiovascular Interventions*, the EUROMAX investigators present an analysis from their important randomized trial (6). They suggest that the use of a continued (4 h) infusion of bivalirudin at the PCI procedure dose is effective in the prevention of AST. This idea has strong biological plausibility, and a similar effect has been reported in the presentation of results from BRIGHT (BivaliRudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa and Heparin: a Randomised Controlled Trial), a Chinese trial—albeit with a different form of bivalirudin and at a lower infusion dose (7).

The EUROMAX investigators have, to their credit, noted that their findings should be treated with caution and cannot be considered as secure without new, prospective trials. This is an important observation. There were only 16 AST events in the study. This makes it very hard to identify the true, independent effect of any individual factor.

Beyond problems with statistical power, the situation is further complicated by the characteristics of patients with an AST event. The vast majority of AST was seen in patients randomized to bivalirudin therapy (12 events vs. 2 events). The rate of GPI use in these bivalirudin-treated AST patients was very high (9 of 12, 75%) when compared with the overall rate of GPI in the bivalirudin arm (12%). This may be related

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to a higher rate of procedural complications reported for these patients. With the low number of absolute events, this may represent the play of chance, but the possibility of a bivalirudin-related, systematic increased rate of procedural issues prompting subsequent AST cannot be excluded.

Interventional cardiologists who are tempted to adopt a strategy of bivalirudin therapy with a continued high-dose infusion (BIV-HIGH) should study the outcome data presented in Table 3 of the paper by the EUROMAX investigators (6), but not highlighted in the text of the report. The BIV-HIGH patients were compared with the patients randomized to heparin. BIV-HIGH therapy provided no significant advantage with respect of any of the primary or secondary outcomes—ischemic major adverse cardiovascular events, bleeding, or combined net clinical benefit measures. Because the numbers in this study are small, it is difficult to draw firm conclusions; however, some reduction in bleeding is counterbalanced by increased major adverse cardiovascular events related to all-cause mortality.

There is also the issue of cost. The cost of bivalirudin therapy is a function of the number of vials purchased, and this will be related to a number of factors, including the body weight of the patient and the duration of the PCI procedure. The systematic use of additional infusions in the pre- and/or post-procedural phases will make the relative cost (compared with heparin) range to more than 1,000 or 1,500 fold. There would also be other cost implications, for example, nursing time. The aim of this investment would be to achieve AST rate equivalence to a drug that costs only pence.

Enthusiasts for bivalirudin believe that the use of this drug reduces bleeding. This advantage has been reported in many studies. The bleeding risk of heparin seems to be related to the rate of concomitant use of glycoprotein IIb/IIIa receptor antagonists and to heparin dosing. In recent studies using lower-dose heparin (70 U/kg body weight) and with "bailout" glycoprotein IIb/IIIa receptor use, bleeding rates are similar to those observed with bivalirudin (3,8).

It is possible that the use of a post-procedural infusion of bivalirudin may abolish the additional stent thrombosis hazard, but any potential trials to examine this question should include a comparator arm using modest-dose heparin therapy and a robust cost-benefit analysis.

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