A second look at bivalirudin

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Direct antithrombins inhibit thrombin in a concentration-dependent fashion without requiring the cofactor antithrombin. Bivalirudin (previously known as hirulog) is a small peptide of 20 amino acids that is a highly potent direct antithrombin. It binds to thrombin in a 1:1 stoichiometric complex simultaneously at exosite 1 (substrate binding domain) and the active catalytic center. Bivalirudin inhibits all known hemostatic and nonhemostatic actions of thrombin, including thrombin-mediated formation of fibrin, activation of platelets, and proliferation of smooth muscle cells. Because bivalirudin acts independently of antithrombin, it remains active even when plasma antithrombin is quantitatively or qualitatively deficient. Bivalirudin escapes neutralization by platelet factors and inhibits both soluble and clot-bound thrombin. Because of its stable antithrombotic effect, bivalirudin may be administered as a constant infusion, and adjustments based on activated partial thromboplastin time measurements are infrequently needed.

Previous clinical experience with bivalirudin in patients with coronary artery disease was encouraging. This included dose-ranging studies in 3 categories of patients, including those undergoing angioplasty, receiving streptokinase for ST elevation myocardial infarction (MI), and receiving treatment for unstable angina. In a systematic overview of all the available clinical trial data with bivalirudin, Kong et al described a significant reduction in the composite outcome of death or nonfatal MI favoring bivalirudin over unfractionated heparin (UFH). This efficacy benefit was seen in conjunction with a significant reduction in major bleeding as well. A mechanistic explanation for the reduction in risk of major hemorrhage with bivalirudin can be found in the drug’s pharmacokinetics. Less than 20% of the administered dose is cleared by renal excretion, minimizing the impact of renal dysfunction on accumulation of high blood concentrations of the drug. Bivalirudin’s binding to thrombin is noncompetitive and reversible in that thrombin slowly cleaves an Arg3-Pro4 bond resulting in re-exposure of the catalytic center of thrombin.

Restoration of the catalytic center of thrombin restores a patient’s hemostatic capacity by promoting the formation of thrombin.

What happened to derail the development of bivalirudin after the initial promising findings? An angioplasty study comparing bivalirudin with UFH was conducted between 1993 and 1994 and reported in 1995. Bivalirudin was found to be at least as effective as high-dose UFH in preventing ischemic complications in patients undergoing angioplasty for unstable angina and was associated with a lower risk of bleeding. Immediate ischemic complications (in hospital) were reduced in the subset of patients undergoing angioplasty for postinfarction angina.

Unfortunately, the results of the angioplasty study were interpreted by the sponsor of bivalirudin at the time as insufficient evidence of an advantage over UFH to warrant the cost of further development of the drug and the decision was made to terminate further clinical studies with bivalirudin. This decision extended to Thrombolysis in Myocardial Infarction (TIMI) 8, a trial of bivalirudin versus UFH for unstable angina that had enrolled 133 of a planned total of 5320 patients, abruptly bringing evaluation of bivalirudin to a halt.

Interestingly, the bivalirudin story has not ended because of a new sponsor and a second look undertaken by several groups of investigators. Some of the authors of the original angioplasty study reported first in 1995 now report in this issue of the Journal a reanalysis of their data. In contrast to the original report that analyzed 4098 patients treated as per protocol (on treatment analysis) the revised report analyzes all 4312 patients randomized (including 214 not receiving treatment). The original report ascertained the primary end point at hospital discharge, a time point that varied from patient to patient. The revised report analyzed the findings at the fixed time points of 7, 90, and 180 days after randomization. The primary efficacy end point of the original report consisted of death, clinical MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin requiring bypass surgery, intra-aortic balloon pumping, or repeat coronary angioplasty. The revised report used a composite primary end point of death, any revascularization, and either clinical or enzymatic (creatine kinase twice normal with abnormal myocardial band values) evidence of MI.

The revised analysis of the angioplasty trial showed statistically significant relative reductions in the incidence of the new primary end point of 22% at 7 days and 18% at 90 days favoring bivalirudin; there was a trend toward a reduction in favor of bivalirudin at 180 days. Major bleeding was significantly reduced by about 65% at all 3 time points. At 7 days the rate of clinically...
significant bleeding was $9.3\%$ in the UFH group and $3.5\%$ in the bivalirudin group ($P < .001$).

How are we to interpret the findings of the revised analysis of the angioplasty trial? It should be recognized that there is a precedent for reanalysis of clinical trial results, for example as reported by the Randomized Efficacy Study of Tirofiban for Outcomes and REStenosis (RESTORE) investigators comparing tirofiban with placebo in the setting of angioplasty. Both the bivalirudin angioplasty investigators and the RESTORE investigators reanalyzed their data using new primary end point definitions that they felt were more in register with the end points used in other trials, arguing that this placed their data on an equal footing compared with other trials. In the case of the bivalirudin angioplasty study, the investigators eliminated angiographic elements of the composite end point and allowed enzymatic evidence of silent MI to be counted as an end point event, a method that is used in angioplasty trials that were conducted subsequent to the original bivalirudin angioplasty study.

By use of the new end point definition it does appear that bivalirudin achieves superiority over UFH and does so with a gratifying safety benefit as well. This is a complicated area, however, and one must not overinterpret the findings. The new end point includes any revascularization rather than target vessel revascularization or urgent revascularization, an approach that has the potential to blur any specific effects of the study drugs on the vessel originally manipulated.

The $9.3\%$ rate of major bleeding with UFH at 7 days occurred with a regimen of a bolus of 175 U/kg and an 18- to 24-hour infusion of 15 U/kg per hour. The target activated clotting time (ACT) in the catheterization laboratory was 350 seconds with a protocol recommendation to administer a bolus of UFH of 60 U/kg if the ACT was below target. Contemporary recommendations for use of UFH to support percutaneous coronary intervention (PCI) procedures in patients not receiving intravenous glycoprotein IIb/IIIa inhibitors call for a bolus of 60 or 70 U/kg to a maximum of 100 U/kg with a target ACT of 250 to 300 seconds with the HemoTec device (Medtronic HemoTec, Englewood, Colo) and 300 to 350 seconds with the Hemochron device (International Technidyne, Edison, NJ). Thus the current use of UFH during PCI involves lower doses than in the bivalirudin angioplasty study and is generally associated with major hemorrhage rates more in the range of $2\%$ than $9.3\%$.

One must also consider the implications of reanalyzing the results of a clinical trial after the findings are reported initially. Clinical trials are the foundation of evidence-based medicine. The results of a trial are often pooled with similar trials in a meta-analysis and may be used by authoritative bodies to formulate guideline documents and recommendations for practice. Imagine the situation if trialists regularly reanalyzed their results with new end point definitions. Therapies that previously were considered not effective might suddenly be “reclassified” as effective if sufficient additional exploratory analyses were performed that found a composite end point showing efficacy for the drug studied. Equally disturbing is the notion of a reanalysis of published trial data that shows a therapy previously considered effective to now be ineffective as judged by new end point definitions. As appropriately acknowledged by the bivalirudin angioplasty investigators, it is unlikely that they would have submitted their revised report for publication if the findings were not favorable for bivalirudin. Thus the possibility of “republication bias” must be considered. We therefore believe reanalysis of clinical trial results should be viewed as hypothesis generating but should not be considered definitive.

Is there any other support for the findings of the revised angioplasty analysis favoring bivalirudin? We analyzed the 133 patients enrolled in the abruptly terminated unstable angina trial (Thrombolysis in Myocardial Infarction [TIMI] 8) that we were conducting. Through 14 days, the incidence of death or nonfatal MI was $9.2\%$ in the 65 patients in the UFH group and $2.9\%$ in the 68 patients in the bivalirudin group, odds ratio (95% CI) $0.30$ ($0.06-1.53$). Major hemorrhage occurred in 3 patients in the UFH group ($4.6\%$) but in none of the patients in the bivalirudin group ($P = .11$). The combination of death, MI, and major hemorrhage occurred in $13.8\%$ of patients in the UFH group and $2.9\%$ of patients in the bivalirudin group ($P = .03$). Thus the findings of the revised angioplasty report and our analysis of the prematurely terminated unstable angina trial are internally consistent and supportive of bivalirudin.

What have these second looks taught us about bivalirudin and the process of drug development? It appears to be at least as effective as UFH in patients with an acute coronary syndrome in a wide variety of settings and may well be superior to UFH. The potential for clinically meaningful antithrombotic activity with a reduced risk for bleeding is particularly attractive. Bivalirudin has been approved by the Food and Drug Administration for use as an anticoagulant in patients with unstable angina undergoing angioplasty. Of note, the package insert describes the data from the original angioplasty report in 1995, not the revised analysis reported in this issue. Thus the decision by the original sponsor of bivalirudin to discontinue its development may have been short sighted.

We believe that the available data underscore the need for further evaluation of bivalirudin. To understand the role of bivalirudin more completely in settings where UFH is used (now with more conservative dosing), properly sized trials need to be conducted in patients who receive contemporary therapy including intravenous glycoprotein IIb/IIIa inhibitors, coronary
stents (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events [REPLACE] trial), and in the case of ST-elevation MI, fibrinolytic therapy with direct plasminogen activators. Certainly, a comparison with heparin in unstable angina/non-ST elevation MI (ie, a contemporary version of the TIMI 8 trial) is now in order.

References