

Accounting for ACUITY

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The treatment of patients with acute coronary syndromes is straightforward in principle but complex in practice. With the increase in referrals of moderate- or high-risk patients for invasive cardiac procedures to improve clinical outcomes,¹ there is a need to define the antithrombotic regimen that is optimal for both stabilizing the underlying active atherosclerotic plaque and minimizing the risk of bleeding.

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, reported in this issue of the *Journal*,² evaluated the role of a thrombin-specific anticoagulant — bivalirudin — as part of a blended medical and invasive strategy for patients with acute coronary syndromes without ST-segment elevation. The study, sponsored by the manufacturer of bivalirudin, randomly assigned 13,819 patients to one of the following three parenteral open-label regimens: control treatment, consisting of heparin (unfractionated heparin or enoxaparin) started before coronary angiography, plus a glycoprotein IIb/IIIa inhibitor started before or during percutaneous coronary intervention (PCI); investigational treatment consisting of bivalirudin started before angiography, plus a glycoprotein IIb/IIIa inhibitor started before or during PCI; and investigational treatment consisting of bivalirudin monotherapy both before and during PCI. Coronary angiography was performed in 99% of patients. Almost all patients received aspirin (98%) and most received clopidogrel (64%) before angiography. Fifty-six percent of patients underwent PCI, 11% required coronary-artery bypass surgery, and 33% received medical therapy alone.

The study defined 11 noninferiority and superiority comparisons by pitting the two investigational groups against the control group and specifying the following three separate primary end points: ischemia (defined as death, myocardial infarction, or unplanned revascularization for ischemia), major bleeding, and the net clinical outcome (defined as the composite of the ischemia end point or bleeding) at 30 days. The noninferiority boundary was prespecified to be 25%, meaning that bivalirudin would be considered noninferior if the one-sided 97.5% confidence interval, corrected for multiple simultaneous comparisons, did not exceed the relative margin of 25% of the event rate for the group receiving heparin. Sequential

superiority testing took place for all comparisons except for the comparison of bivalirudin monotherapy with the control treatment for the analysis of the ischemia end point.

The main results of the ACUITY trial are clear. The nominal 7% decrease in bleeding events seen with bivalirudin plus a glycoprotein IIb/IIIa inhibitor offset the nominal 7% increase in ischemic events, which resulted in a near-perfect balance in the composite event rates and corresponded to an absolute difference of 0.1 percentage point from the control group. The significant 47% reduction in bleeding seen with bivalirudin monotherapy offset the noninferior 8% increase in ischemic events and produced a small significant 14% reduction in net clinical outcomes at 30 days, which corresponded to an absolute decrease of 1.6 percentage points from the control group.

An equivalence trial such as the ACUITY trial requires a more cautious interpretation than a conventional superiority trial. Most superiority trials of antithrombotic therapies for acute coronary syndromes have detected small but statistically significant treatment effects with the use of biomarkers to show evidence of myocardial injury as the pivotal component of composite end points.³⁻⁵ In contrast, the ACUITY trial did not identify a significant reduction in ischemic events with bivalirudin but instead relied on the determination that bivalirudin is noninferior to heparin for this end point.

However, the reduction in bleeding events with the use of bivalirudin alone was statistically significant. Bleeding is the most serious unintended consequence of antithrombotic therapy for acute coronary syndromes and may have greater prognostic significance than biomarker positivity for one-year survival after PCI.⁶ Several studies have shown that, as compared with other antithrombotic agents, bivalirudin reduces the risk of bleeding during medical therapy⁷ and after invasive procedures.^{6,8,9} The safety profile of bivalirudin probably relates to its pharmacokinetics and the observation that an extended anticoagulant effect after PCI increases bleeding but provides no protection against ischemia.¹⁰ Bivalirudin has a plasma half-life of 25 minutes, unfractionated heparin has a longer dose-dependent half-life, and the low-molecular-weight heparins have half-lives that range from 2 to 4 hours after intra-

venous injection and from 3 to 6 hours after subcutaneous injection.¹¹

Published guidelines for the medical management of acute coronary syndromes without ST-segment elevation recommend the combined use of aspirin, clopidogrel, intravenous glycoprotein IIb/IIIa inhibitors, and unfractionated or low-molecular-weight heparin.¹² The results of the ACUITY trial extend preliminary observations^{7,13} and suggest that bivalirudin could replace heparin for the initial treatment of patients with acute coronary syndromes managed with an intended invasive strategy. Published guidelines for PCI, based on the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2) trial,⁹ state that bivalirudin monotherapy can substitute for heparin plus glycoprotein IIb/IIIa inhibitors in low-risk elective procedures¹⁰ and possibly for patients with myocardial infarctions without ST-segment elevation.¹⁴ A larger proportion of patients who had myocardial infarctions without ST-segment elevation were in the ACUITY trial (59%) and in another confirmatory trial (49%)⁸ than were in the REPLACE-2 trial (8%).⁹ Future guidelines may endorse bivalirudin as a substitute for heparin plus glycoprotein IIb/IIIa inhibitors in high-risk patients.

One caveat of the ACUITY trial was identified in a prespecified subgroup analysis. Patients assigned to bivalirudin monotherapy who were not pretreated with clopidogrel had a significant 29% increase in ischemic events as compared with those treated with a glycoprotein IIb/IIIa inhibitor. This finding suggests, but does not prove conclusively, that patients treated with bivalirudin monotherapy should be pretreated with clopidogrel in a dose of 300 mg 6 hours before PCI,¹⁰ but a dose of 600 mg as early as 2 hours before PCI remains controversial.¹⁵ Patients who require urgent PCI but have not been adequately pretreated with aspirin or clopidogrel should receive a glycoprotein IIb/IIIa inhibitor.

A noninferiority trial like the ACUITY trial, which was designed to test multiple composite outcomes, could be criticized as a shell game. The significance of the study, however, is its unique ability to evaluate the integrated antithrombotic and invasive therapies used in the contemporary treatment of patients with acute coronary syndromes. The ACUITY trial provides strong support for the use of bivalirudin as a substitute for heparin plus glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes who un-

dergo early invasive management, in particular if they are pretreated with clopidogrel.

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