EDITORIAL

Procedural Anticoagulation in Myocardial Infarction

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The prognosis for patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) is improved with the use of percutaneous coronary intervention (PCI). Choosing the best procedural anticoagulation regimen to balance the risks of ischemia and bleeding during PCI is essential to optimize outcomes. Heparin, a nonspecific indirect thrombin inhibitor, was the only anticoagulant agent used during PCI for several decades, first with aspirin alone and then with aspirin plus a platelet $P2Y_{12}$ receptor inhibitor (ticlopidine or clopidogrel). Adding a platelet glycoprotein IIb/IIIa receptor inhibitor to heparin therapy further reduced the risk of stent thrombosis, reinfarction, and death among patients undergoing PCI for STEMI but increased the risk of major bleeding.[1] Despite the increase in the risk of bleeding, heparin plus a glycoprotein IIb/IIIa inhibitor became the most widely used regimen during PCI in the United States because of the associated reduction in the risk of thrombotic events.

The direct thrombin inhibitor bivalirudin was first introduced as an alternative to heparin in the 1990s and was approved by the Food and Drug Administration in 2000. Randomized trials subsequently showed that, among patients undergoing PCI for NSTEMI or STEMI, the risk of major bleeding was lower with bivalirudin alone than with heparin plus a glycoprotein IIb/IIIa inhibitor; the two regimens were associated with similar rates of cardiovascular events.[2-4] As such, bivalirudin succeeded heparin as the dominant anticoagulant used during PCI in the United States.

Most physicians in Europe preferred to use heparin alone during PCI. This practice was reinforced by two advances. The first was the introduction of more potent and rapid-acting $P2Y_{12}$ inhibitors (ticagrelor and prasugrel), which result in a risk of ischemic complications after PCI for myocardial infarction that is lower than the risk with clopidogrel (although the more potent $P2Y_{12}$ inhibitors also increase the risk of major bleeding). The second was the use of radial-artery access for PCI, which is associated with a risk of bleeding at the access site that is lower than the risk with femoral-artery access. In a single-center trial of PCI performed with the use of these enhancements and with a low rate of the use of glycoprotein IIb/IIIa inhibitors, rates of bleeding among patients with STEMI did not differ significantly between the bivalirudin group and the heparin group.[5] However, multicenter trials of PCI performed with high rates of the use of radial-artery access, potent $P2Y_{12}$ inhibitors, or both generally showed lower rates of bleeding but also higher rates of stent thrombosis with bivalirudin therapy than with heparin therapy among patients with STEMI.[6-8]

To address these ongoing uncertainties, Erlinge and colleagues performed VALIDATE-SWEDEHEART (Bivalirudin versus Heparin in ST-Segment and Non–ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies Registry Trial), in which 6006 patients in Sweden who were undergoing PCI for NSTEMI or STEMI were randomly assigned to receive procedural anticoagulation with either bivalirudin or heparin alone.[9] At 6 months, the primary composite end point of death, myocardial infarction, or major bleeding had occurred in 12.3% of the patients in the bivalirudin group and in 12.8% in the heparin group (hazard ratio, 0.96; 95% confidence interval, 0.83 to 1.10; P=0.54). In contrast to the results of many earlier studies, the rate of major bleeding was not significantly lower and the rate of stent thrombosis was not significantly higher with bivalirudin therapy than with heparin therapy. The authors speculate that the frequent use of the radial approach (in 90% of the patients) and the low use of glycoprotein IIb/IIIa inhibitors (in 3%) mitigated

the advantage of bivalirudin with respect to the risk of bleeding. In addition, they speculate that treatment with potent $P2Y_{12}$ inhibitors (in 97% of the patients) and prolonged infusion of bivalirudin during PCI (in 65% of the patients in the bivalirudin group) ameliorated the risk of acute stent thrombosis associated with bivalirudin anticoagulation that had been seen in some previous studies.

Some limitations of VALIDATE-SWEDEHEART should be noted. The observed event rates were lower than anticipated, and the low event rates resulted in a wide confidence interval around the 6-month point estimate for the primary end point. At 30 days (which is a better time point than 6 months at which to compare procedural anticoagulants), a nonsignificant trend in favor of bivalirudin was evident. Moreover, the primary end point was a composite of safety and efficacy measures, which tend to offset one another and could therefore bias outcomes toward the null. Most patients who received bivalirudin (91%) also received a substantial amount of heparin (mean dose before and during PCI, 3470 U), which may have further minimized differences between the groups. The trial was not powered to examine the individual components of safety and efficacy, including death.

The rate of the primary end point was consistent between patients with STEMI and those with NSTEMI, but data regarding death, bleeding, and stent thrombosis were not reported separately for each clinical syndrome. STEMI is associated with greater platelet activation and thrombus burden, a lower volume of coronary blood flow, and larger infarctions than is NSTEMI. A meta-analysis of six randomized trials conducted before VALIDATE-SWEDEHEART that compared bivalirudin therapy with heparin therapy, with or without the use of glycoprotein IIb/IIIa inhibitors, among a total of 14,095 patients with STEMI showed that bivalirudin was associated with a lower rate of major bleeding, a higher rate of stent thrombosis, and an 18% lower 30-day mortality than was heparin.[10] The lower mortality with bivalirudin was consistent across all six trials, regardless of the use of femoral-artery versus radial-artery access, routine versus provisional use of glycoprotein IIb/IIIa inhibitors, differing bivalirudin infusion regimens, and the use of $P2Y_{12}$ inhibitors of various potencies. In contrast, previous trials involving patients with NSTEMI showed rates of death, myocardial infarction, and stent thrombosis that were similar with bivalirudin and heparin, although they showed lower rates of bleeding with bivalirudin than with heparin.[2,3,8]

Thus, even after VALIDATE-SWEDEHEART, there is no definitive answer to the question of whether to use bivalirudin or heparin during PCI. To provide more power in examining individual safety and efficacy outcomes and to overcome the limitations inherent in summary-level meta-analysis, the principal investigators of each of the large-scale randomized trials comparing bivalirudin with heparin for myocardial infarction (including VALIDATE-SWEDEHEART) have agreed to combine the individual patient data from their studies into a single database. Detailed data from more than 36,000 patients randomly assigned to bivalirudin or heparin should provide robust evidence to guide decisions regarding anticoagulation among patients with STEMI and NSTEMI according to various patient characteristics, procedures, and adjunct pharmacotherapies.

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