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EDITORIAL COMMENT

Does Enoxaparin Have Enough FINESSE to Replace Unfractionated Heparin in Primary Percutaneous Coronary Intervention?*

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Acute ST-segment elevation myocardial infarction (STEMI) is caused by coronary plaque disruption with exposure of substances that promote platelet activation, adhesion, and aggregation; thrombin generation; and thrombus formation leading to an occluded infarct-related artery (IRA) (1). Thus, patients presenting with STEMI receive reperfusion therapy—either fibrinolysis or primary percutaneous coronary intervention (PCI)—to restore coronary flow, limit myocardial necrosis, and improve clinical outcomes (2–4). Even if adequate restoration of flow with reperfusion therapy is established in the epicardial IRA, perfusion of the infarct zone might still be compromised. Microvascular damage occurs in part as a consequence of downstream embolization of platelet microemboli and thrombi followed by release of substances from activated platelets that promote occlusion or spasm. Adjunctive antithrombotics are therefore critical to maintain IRA patency (decreasing thrombus accretion and preventing reocclusion) and potentially minimize microvascular damage (2).

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The vast majority of clinical trial evidence supporting guideline recommendations (2–4) for the use of antiplatelet and anticoagulant therapies in STEMI has come from patient populations receiving fibrinolytic therapy; however, primary PCI has been demonstrated to be superior to fibrinolysis in reducing mortality when it can be performed rapidly (5), such that primary PCI is the preferred reperfusion strategy whenever feasible (3,4). Importantly, the goals of antithrombotic therapy for primary PCI differ somewhat from those for fibrinolysis, which fails to restore IRA patency or is associated with a risk for early reocclusion in approximately 20% of patients (6); the main focus of anticoagulant therapy in primary PCI is the minimization of thrombotic complications related to the mechanical intervention. Although unfractionated heparin (UFH) is the only Class/Grade I-recommended acute anticoagulant therapy in primary PCI (2–4), the weight/level of evidence is "C," reflecting mainly a consensus of opinion of the experts rather than guidance from randomized trial data.

Potential alternatives to UFH in STEMI patients undergoing PCI have been explored. The indirect factor Xa inhibitor fondaparinux was compared with UFH in a subgroup of STEMI patients undergoing primary PCI in the OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes-6) study (7), and there was a numeric increase in the composite of death or reinfarction among fondaparinux-treated patients that occurred in the setting of a higher rate of guiding catheter thrombosis and more coronary complications. Thus, in the setting of primary PCI, fondaparinux is not recommended (2–4).

The direct thrombin inhibitor bivalirudin was compared with UFH plus glycoprotein IIb/IIIa inhibitors in patients undergoing primary PCI in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial (8). Treatment with bivalirudin resulted in a significantly lower 30-day rate of net adverse clinical events, due to a lower rate of major bleeding, but with similar rates of major adverse cardiovascular events (although death at 30 days was significantly lower). However, the minority of patients received bivalirudin monotherapy (6), and although the 30-day net clinical end point was relatively reduced in the bivalirudin-treated patients who received pre-randomization UFH, there was a relative increase in events in the bivalirudin-treated patients who did not receive antecedent UFH. Together with the increased risk for early stent thrombosis, these findings have led to a lower class of recommendation for bivalirudin as the sole anticoagulant in primary PCI (4).

Previously, data in the setting of primary PCI with enoxaparin have been limited to anti-Xa level findings in a small prospective registry (9) and clinical trial subgroup (10). Montalescot et al. (11) now provide substantial additional information regarding enoxaparin in primary and facilitated PCI (with abciximab or abciximab plus half-dose fibrinolysis) as part of a nonrandomized substudy of the FINESSE (Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events) trial (12). Each enrolling center prespecified its choice of either UFH or enoxaparin as the adjunct anticoagulant therapy; 759 from 42 centers were included in the enoxaparin substudy, and 1,693 from

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170 centers received UFH. There was reasonable adherence to the intended anticoagulation strategy (e.g., 93% of patients received enoxaparin) with limited cross-over (e.g., 2% received UFH in addition to enoxaparin).

Because the substudy focused on a nonrandomized comparison between enoxaparin and UFH, it is not surprising that the 2 "treatment" groups were not comparable. For example, UFH-treated patients were more frequently enrolled at PCI-capable hospitals in Western Europe and had longer times from symptom onset to balloon; they were also more likely to have received aspirin but less likely to have received clopidogrel or ticlopidine before randomization. In an attempt to adjust for multiple risk factors and potential imbalance of other factors, logistic regression modeling and propensity score methodology were employed.

Nonintracranial hemorrhage major bleeding was lower in enoxaparin-treated patients, but minor bleeding was more frequent. Intracranial hemorrhage was rare and not different in the 2 groups. Although the FINESSE primary composite end point (all-cause mortality or complications of myocardial infarction) through 90 days was similar in the 2 anticoagulant groups, there was a lower risk of the composite of death or reinfarction at 30 days and all-cause mortality at 90 days with enoxaparin. These findings were particularly apparent in the subset of patients (n = 806) who underwent primary PCI; indeed, this might be the most relevant subgroup given the lack of benefit and potential harm of the strategy of facilitated PCI compared with primary PCI (13).

Thus, enoxaparin was associated with a lower risk of cardiovascular outcomes and major bleeding (but with more minor bleeding) when compared with UFH in STEMI patients undergoing primary PCI (11). Importantly, although the primary safety end points and secondary efficacy end points were pre-specified, there was no formal statistical adjustment made for multiple comparisons in this unblinded, observational, hypothesis-generating substudy. Although providing the largest experience of enoxaparin in primary PCI, the FINESSE substudy does not provide practice- or guideline-changing results—indeed, UFH should remain the anticoagulant of choice in the setting of primary PCI at present. However, Montalescot et al. are currently seeking to confirm the hypothesis raised by their FINESSE findings in a randomized, clinical outcome trial comparing IV enoxaparin (0.5 mg/kg) with UFH (50 to 70 U/kg with or 70 to 100 U/kg without glycoprotein IIb/IIIa inhibition). The ATOLL (Acute STEMI Treated with primary angioplasty and intravenous enoxaparin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up) study results are anticipated in late 2010, at which time we will learn whether enoxaparin is truly a better alternative to UFH in primary PCI.

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