Substitution of Fractionated for Unfractionated Heparin During High-Risk Percutaneous Coronary Intervention

Has the Problem Been Solved?*

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Percutaneous coronary intervention (PCI) is frequently performed in patients who received fibrinolytic therapy for acute myocardial infarction (MI). Currently, unfractionated heparin is the most commonly used antithrombin therapy in this situation. However, unfractionated heparin has certain limitations. It has a narrow therapeutic range, monitoring of the activated clotting time is required, and platelet activation may be induced. For these reasons, considerable interest has been generated around the question of whether low-molecular-weight heparin can be used in place of unfractionated heparin in the context of high-risk PCI. Low-molecular-weight heparin provides a more dependable anticoagulation response than unfractionated heparin, it has greater antifactor Xa:antifactor IIa activity, and it is less likely to induce platelet activation (1). Importantly, however, cases have been reported of catheter- and guidewire-associated thrombosis during PCI procedures in conjunction with the use of low-molecular-weight heparin (2,3). Results from the STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention [PCI] Patients: an International Randomized Evaluation) trial suggest that, when used during elective PCI in low-risk patients, enoxaparin has similar or lower rates of bleeding compared with unfractionated heparin (1). Unfortunately, the STEEPLE trial was not large enough to provide definitive information about ischemic events and procedure-related thrombotic events. To date, we have only limited data available regarding the safety and efficacy of low-molecular-weight heparin when used during PCI in high-risk patients.

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In this issue of the Journal, Gibson et al. (4) report the results of the PCI substudy from the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) trial. In that trial (5), over 20,000 patients who received fibrinolytic therapy for ST-segment elevation myocardial infarction (STEMI) were randomized to unfractionated heparin for at least 48 h versus enoxaparin for the duration of the index hospitalization. In the substudy performed by Gibson et al. (4), data are reported on the more than 2,200 patients who underwent PCI in the enoxaparin arm of the trial and the more than 2,400 patients who underwent PCI in the unfractionated heparin arm. The investigators found that treatment with enoxaparin was associated with a reduction in death or recurrent MI and no difference in major bleeding. They conclude that the use of enoxaparin in the context of PCI after fibrinolytic therapy is superior to the use of unfractionated heparin. The authors are to be congratulated on reporting the results of their study. Until this report, there were very little data available to guide cardiologists with respect to whether low-molecular-weight heparin is as safe and efficacious as unfractionated heparin during PCI in this high-risk group of patients. However, several potential limitations of their study should be noted.

First, only a small proportion of the patients who received fibrinolytic therapy in the ExTRACT-TIMI 25 trial subsequently underwent PCI, and this subgroup of patients was not directly randomized to enoxaparin versus unfractionated heparin. Although the investigators report that the clinical characteristics of the PCI patients who received enoxaparin and unfractionated heparin were similar, this is not the same as direct randomization. Using propensity scores can help control for confounding in this situation, but it cannot completely control for this possibility (6). This problem is further compounded by the facts that treatment durations were very different among patients receiving enoxaparin and unfractionated heparin and that, by the time of PCI, antithrombin treatment had been unblinded for the majority of the patients.

A second potential limitation is the relative lack of information that is provided about the PCI procedures themselves. We are not presented with information such as numbers of patients who received pretreatment with clopidogrel, the numbers of patients who underwent multivessel...
PCI, the numbers of patients who received stents—both drug-eluting and bare-metal—and the numbers of patients who experienced procedure-related thrombosis. What was the mean time between the MI and the PCI? What were the rates of use of rescue PCI? How many patients had radial procedures? What were the rates of use of closure devices? The low rate of clopidogrel use suggests that a high proportion of patients underwent simple balloon angioplasty rather than stenting. All of the aforementioned issues could potentially impact on the generalizability of the study results to practice in North America.

Third, the recently published results from OAT (O-ccluded Artery Trial) suggest that there is often little benefit to late PCI in patients who do not reperfuse after STEMI (7). How many of the patients in this substudy fell into that category? Although most patients in North America undergo PCI relatively soon after they receive fibrinolytic therapy, it appears that many of the patients in the PCI substudy of ExTRACT-TIMI 25 may have been OAT-type patients, patients in whom there is now little evidence of a benefit from PCI.

Finally, there have been several alarming reports of catheter- and guidewire-associated thrombosis in the setting of PCI when low-molecular-weight heparin is used (2,3). Because of these reports, many clinicians still feel uncomfortable performing PCI in high-risk patients with low-molecular-weight heparin. Although the study by Gibson et al. is reassuring in this regard, many clinicians will want more definitive data before making the switch.

Thus, although the results reported by Gibson et al. (4) are virtually the only data available in this subgroup of patients, I do not believe that it gives us a definitive answer as to whether enoxaparin can be safely substituted for unfractionated heparin during high-risk PCI. To provide the needed data, a clinical trial in which high-risk patients undergoing PCI are directly randomized, in a blinded manner, to 2 treatment arms, and in which the 2 treatment arms are of similar duration, is required.

Despite the potential limitations noted above, I think that the study by Gibson et al. (4) makes an important contribution to the literature. The results suggest that low-molecular-weight heparin may ultimately prove to be safe and efficacious as an adjunct to PCI after fibrinolytic therapy for STEMI. These results are important, given that antithrombin therapy after successful fibrinolysis is often selected by physicians who are not involved in the subsequent invasive cardiac care of the patient.

Future directions in this area will involve the investigation of other antithrombin therapies. For example, direct thrombin inhibitors such as bivalirudin have been shown to be effective during PCI in low-risk patients, are cheaper than the combination of low-molecular-weight heparin or unfractionated heparin with glycoprotein IIb/IIIa inhibitors (8), and may ultimately prove to be effective in high-risk patients as well.

Regarding the question as to whether we should substitute fractionated for unfractionated heparin during PCI in high-risk patients, I think that the problem still awaits a definitive solution.

Acknowledgments
The author thanks Drs. Dominique Joyal and Stephane Rinfret for their helpful comments.

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