Anticoagulation for ST-Segment Elevation Myocardial Infarction

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Adjunctive anticoagulant therapy reduces the risk of recurrent infarction and death in patients with ST-segment elevation myocardial infarction (STEMI) receiving fibrinolytic therapy. Unfractionated heparin (UFH), the first anticoagulant evaluated for this indication, continues to be used because of its predominantly nonrenal clearance, short half-life, reversibility, and the familiarity of clinicians with the drug. However, the anticoagulant response to UFH is unpredictable, which necessitates coagulation monitoring, and the time to achieve a therapeutic anticoagulant effect can vary from patient to patient. This is problematic because failure to achieve a therapeutic anticoagulant effect with UFH has been associated with an increased risk of recurrent ischemic events.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Why did so many patients fail to achieve a therapeutic aPTT 4 to 8 hours after starting UFH despite the use of a standardized weight-based nomogram? Unlike the validated weight-based UFH-dosing nomogram used for the management of venous thromboembolism,18 the ACC/AHA-recommended UFH nomogram8,9 and the protocol used for subsequent dose adjustments have not been prospectively validated in patients with STEMI. At the very least, the fact that body weight is a significant predictor of a markedly high or low initial aPTT suggests that the ACC/AHA-
recommended nomogram does not adequately adjust for this factor.

The results of the study by Cheng et al provide a framework for the development of a modified heparin-dosing nomogram that incorporates age, sex, and creatinine. Standardization of the aPTT assay, as was accomplished in this study, might also improve the effectiveness of UFH therapy but would not overcome the imprecision caused by biological variables that interfere with the aPTT dose-response to UFH. Although it may be better to replace the aPTT with the anti-factor Xa assay, which provides a more direct measure of UFH concentration and is unaffected by biological variables, anti-factor Xa assays are expensive and are not widely available. Will this study prompt the development and validation of new approaches to UFH delivery in STEMI patients? This is unlikely to occur because UFH is increasingly being replaced by newer more effective anticoagulant strategies (Table).

What are the implications of the findings by Cheng and colleagues for clinical practice? The study highlights the fact that UFH has limitations which reduce its efficacy and compromise its safety when used for the treatment of patients with STEMI. These findings should prompt clinicians to consider using alternative anticoagulants that have been proven to be effective for the treatment of STEMI. Although intravenous UFH has never been shown to reduce reinfarction or death in STEMI patients, randomized controlled trials in such patients treated with fibrinolytic therapy reveal that (a) both reviparin, a low–molecular-weight heparin, and fondaparinux reduce mortality when compared with placebo or conventional therapy, and (b) enoxaparin reduces reinfarction by about one half compared with UFH.1 In STEMI patients undergoing primary percutaneous coronary intervention, the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial demonstrated that bivalirudin plus provisional glycoprotein IIb/IIIa inhibitor therapy significantly reduced both mortality and bleeding compared with UFH plus a glycoprotein IIb/IIIa inhibitor.5 Although the extent to which the variability of the anticoagulant response to UFH differs in the duration of treatments might have contributed to the superiority of enoxaparin and bivalirudin in the randomized comparisons is uncertain, low–molecular-weight heparin and fondaparinux are effective alternatives to UFH in STEMI patients treated with fibrinolytic therapy, whereas bivalirudin is an attractive alternative to UFH in those undergoing primary percutaneous coronary intervention.

Because many of the newer anticoagulants are cleared through the kidneys, have a longer half-life than UFH, and/or lack antidotes, UFH will continue to be the anticoagulant of choice for patients with renal failure and UFH will still be used in the critical care setting for patients at high risk for bleeding or for those requiring frequent interventions. A potential replacement for UFH in these settings is the factor Xa–directed RNA aptamer. This drug produces a rapid and predictable anticoagulant response that can be readily neutralized by administration of an inhibitory complementary aptamer.20 Trials evaluating the efficacy and safety of this promising drug-antidote pair are ongoing.

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