Anticoagulation for ST-Segment Elevation Myocardial Infarction

John W. Eikelboom, MD; Jeffrey I. Weitz, MD

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.

In this edition of Circulation, Cheng and colleagues report the results of their study exploring the clinical predictors of initial nontherapeutic anticoagulation with UFH in a subset of 6055 patients with STEMI enrolled in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment—Thrombolysis in Myocardial Infarction (ExTRACT-TIMI)—25 trial. In this patient subset, UFH was given as an initial bolus dose of 60 U/kg (maximum 4000 U) followed by an intravenous infusion of 12 U/hr (maximum 1000 U/hr) according to the American College of Cardiology/American Heart Association (ACC/AHA)—recommended weight-based nomogram. Subsequent UFH dose adjustments, which were standardized via a central interactive voice response system, were based on the results of the activated partial thromboplastin time (aPTT). The trial protocol mandated continuation of UFH for a minimum of 48 hours. Patients in whom the UFH infusion was interrupted before the first aPTT measurement (4 to 8 hours after commencement of the infusion) and those who received UFH before randomization were excluded from the analysis.

After 4 to 8 hours of UFH treatment, only one third (33.8%) of the patients included in the study had an aPTT within the target therapeutic range (1.5 to 2.0× control) and about one third (29.5%) had either markedly low (<1.25× control) or markedly high (≥2.75× control) aPTT values. Increasing age, female sex, decreasing body weight, and increased serum creatinine were associated with an elevated aPTT; older, female, and lighter patients and those with higher creatinine levels were more likely to have a markedly high aPTT after 4 to 8 hours, and younger, female, and heavier patients were more likely to have a markedly low aPTT. A correlation was found between aPTT and clinical outcome. Thus, patients with a markedly high aPTT had an ~2-fold increased risk of TIMI major or minor bleeding compared with those with a therapeutic aPTT 4 to 8 hours after starting UFH, whereas those with a markedly low aPTT had an ~2-fold higher risk of recurrent myocardial infarction during the first 48 hours.

An association between a subtherapeutic aPTT and the risk of recurrent thrombosis has been reported in patients with venous thromboembolism, although such a relationship was less evident in studies where patients received adequate initial and maintenance doses of UFH. Although an association between a subtherapeutic aPTT and reinfarction has also been reported in patients with arterial thrombosis, this has not been a consistent finding. Possible explanations for these divergent results include that the therapeutic range for the aPTT is poorly defined and the aPTT is an imprecise measure of the anticoagulant intensity of UFH. Less than 50% of the variability in plasma UFH concentrations is demonstrable by the aPTT, with the remaining variability explained by preanalytic (eg, method of sample collection and processing), analytic (eg, reagent and coagulometer used to measure the aPTT), and biological (eg, increased levels of factor VIII or reduced levels of antithrombin) factors that alter the dose response of the aPTT to heparin. Nonetheless, Cheng and colleagues were able to show a clear association between failure to achieve a therapeutic aPTT and the risk of recurrent infarction and bleeding, possibly because they minimized the variability caused by preanalytical factors by using whole blood in place of plasma and they eliminated variability due to analytic factors by using a standardized point-of-care aPTT assay in all patients.

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, the ACC/AHA-recommended UFH nomogram 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-
Table. Comparison of the Pharmacology of UFH and Newer Parenteral Anticoagulants

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Administration</th>
<th>Half Life, h</th>
<th>Predictability of Anticoagulant Response</th>
<th>Need for Monitoring</th>
<th>Clearance</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>Intravenous</td>
<td>1–2</td>
<td>Unpredictable</td>
<td>Yes</td>
<td>Hepatic; RES (minor); renal (minor)</td>
<td>Yes, protamine</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Subcutaneous*</td>
<td>4–6</td>
<td>Predictable</td>
<td>No</td>
<td>Renal</td>
<td>Partial, protamine</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Subcutaneous</td>
<td>17–21</td>
<td>Predictable</td>
<td>No</td>
<td>Renal</td>
<td>No</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Intravenous</td>
<td>1</td>
<td>Predictable</td>
<td>No</td>
<td>Proteolytic cleavage; renal (20%)</td>
<td>No</td>
</tr>
<tr>
<td>Factor IXa–directed aptamer</td>
<td>Intravenous</td>
<td>Variable</td>
<td>Predictable</td>
<td>Uncertain</td>
<td>Extrarenal</td>
<td>Yes, complementary aptamer</td>
</tr>
</tbody>
</table>

RES indicates reticulo-endothelial system.
*First dose given intravenously.

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,4,19 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.9 Although the extent to which the variability of the anticoagulant response to UFH or differences 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 IXa–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.

Disclosures

Dr Eikelboom has received grant support and honoraria from Glaxo-Smith-Kline and sanofi-aventis. Dr Weitz has received honoraria from sanofi-aventis and The Medicines Company.

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