Randomized Comparison of Enoxaparin, a Low-Molecular-Weight Heparin, With Unfractionated Heparin Adjunctive to Recombinant Tissue Plasminogen Activator Thrombolysis and Aspirin Second Trial of Heparin and Aspirin Reperfusion Therapy (HART II)

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Background—Adjunctive unfractionated heparin (UFH) during thrombolytic therapy for acute myocardial infarction (AMI) promotes the speed and magnitude of coronary artery recanalization and reduces reocclusion. Low-molecular-weight heparins offer practical and potential pharmacological advantages over UFH in multiple applications but have not been systematically studied as adjuncts to fibrinolysis in AMI.

Methods and Results—Four hundred patients undergoing reperfusion therapy with an accelerated recombinant tissue plasminogen activator regimen and aspirin for AMI were randomly assigned to receive adjunctive therapy for at least 3 days with either enoxaparin or UFH. The study was designed to show noninferiority of enoxaparin versus UFH with regard to infarct-related artery patency. Ninety minutes after starting therapy, patency rates (thrombolysis in myocardial infarction [TIMI] flow grade 2 or 3) were 80.1% and 75.1% in the enoxaparin and UFH groups, respectively. Reocclusion at 5 to 7 days from TIMI grade 2 or 3 to TIMI 0 or 1 flow and TIMI grade 3 to TIMI 0 or 1 flow, respectively, occurred in 5.9% and 3.1% of the enoxaparin group versus 9.8% and 9.1% in the UFH group. Adverse events occurred with similar frequency in both treatment groups.

Conclusions—Enoxaparin was at least as effective as UFH as an adjunct to thrombolysis, with a trend toward higher recanalization rates and less reocclusion at 5 to 7 days. (Circulation. 2001;104:648-652.)

Key Words: myocardial infarction — thrombolysis — reperfusion — heparin — trials

The utility of fibrinolytic agents plus effective adjunctive antithrombotic therapy in the treatment of acute myocardial infarction (AMI), particularly in combination with fibrin-selective plasminogen activators, is well established.1–10 Specifically, the use of antithrombotic drugs, traditionally unfractionated heparin (UFH), and aspirin are intended to decrease the phenomenon of new fibrin formation during the lytic process.

Thrombin activity is enhanced after AMI and plays a key role in promoting thrombus formation. Paradoxically, the use of thrombolytic drugs enhances prothrombotic processes by releasing a pool of trapped thrombin during the course of clot lysis and directly activating platelets.9,11,12 A potential limitation of the therapeutic benefit of UFH is suggested by data from the Global Utilization of Streptokinase and t-PA for Ooccluded arteries–I (GUSTO-I) trial, demonstrating that although UFH impedes thrombin activity associated with thrombolysis, it does not inhibit thrombin generation, which in turn predicts subsequent thrombotic events.13 Agents that inhibit coagulation factors earlier in the coagulation cascade may therefore prove more effective than UFH as adjuncts to thrombolytic therapy. A further disadvantage of UFH is the difficulty in maintaining therapeutic plasma levels, necessitating frequent monitoring and dose adjustment. Even so, dosing of UFH may be suboptimal in ≥50% of cases, based on measurements of the activated partial thromboplastin time (aPTT).14 Low-molecular-weight heparins (LMWHs), such as enoxaparin, may offer important advantages over UFH as adjuncts to thrombolysis after AMI because of a higher anti-factor Xa:IIa ratio (3:1 versus 1:1) and a more predictable bioavailability.15,16

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LMWHs have been investigated in several clinical circumstances, particularly the treatment of unstable angina and non-Q-wave myocardial infarction. In such patients, enoxaparin has been demonstrated to be superior to UFH in preventing death, AMI, and recurrent angina, without increasing the risk of bleeding. Despite these encouraging findings, few studies have investigated the use of LMWHs as antithrombotic adjuncts to thrombolysis. The current study, the Second trial of Heparins and Aspirin Reperfusion Therapy (HART II), was designed to clarify the potential role of enoxaparin as an alternative to UFH as an adjunct to thrombolysis in the emergency treatment of AMI.

Methods

The HART II trial was a multicenter, international, phase II clinical study with an open-label, parallel-group, randomized design. The trial was powered to demonstrate noninferiority of enoxaparin versus UFH in the treatment of AMI with regard to the initial patency assessed at 90 minutes. Patients were ≥18 years of age and had no contraindications to thrombolytic therapy. All had ischemic symptoms of ≥30 minutes' duration and met the following ECG criteria: ST-segment elevation ≥0.1 mV in ≥2 limb leads or ST-segment elevation ≥0.2 mV in ≥2 contiguous precordial leads. All patients were treated within 12 hours of the onset of symptoms. The study design is summarized in Figure 1. Patients with serum creatinine of ≥2 mg/dL per liter were excluded.

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committees of all participating institutions.

After enrollment, patients received aspirin and underwent thrombolysis with recombinant tissue-type plasminogen activator (rt-PA; allepase recombinant obtained from Genentech and Boehringer Ingelheim), with the accelerated infusion regimen (15-mg intravenous bolus, then 0.75 mg/kg intravenously over a period of 30 minutes (maximum, 50 mg), then 0.5 mg/kg intravenously over a period of 60 minutes (maximum 35 mg), total dose not exceeding 100 mg). Patients randomly allocated to enoxaparin received an initial 30-mg intravenous bolus followed by 1 mg/kg SC every 12 hours. The intravenous bolus dose was selected on the basis of the HART II pilot study, in which patients receiving an intravenous dose of 30 mg followed by a 0.75 mg/kg three times daily of enoxaparin achieved therapeutic anti-Xa activity levels within 30 minutes. The 1 mg/kg twice daily SC dose was selected on the basis of the experience gained by using this dosage in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and Thrombolysis In Myocardial Infarction (TIMI) IIA studies, in which the 1 mg/kg SC dose was safe and efficacious in preventing recurrent ischemia in unstable angina and patients with non–ST-segment elevation myocardial infarction. Patients in the UFH (obtained from Fujisawa) group received an initial intravenous bolus (4000 U for those weighing up to 67 kg; 5000 U for patients ≥67 kg), followed by an infusion of 15 U/kg per hour for at least 3 days, adjusted to achieve a target aPTT of 2 to 2.5 times control. Coronary angiography was performed 90 minutes after the initial bolus rt-PA dose and repeated for reocclusion assessment after 5 to 7 days.

This trial was conducted between January 1999 and January 2000, a period during which sheath management was changing rapidly. Interventionists were shifting from long delays to short ones (end of procedure to sheath removal), and closure devices were coming into use. The protocol recommended for UFH patients that the sheath was removed ~6 hours after insertion; for those receiving enoxaparin, it was recommended that the sheath was left until 6 to 8 hours after a dose of enoxaparin.

The primary trial objective was to demonstrate noninferiority of enoxaparin versus intravenous UFH in efficacy measured by the 90-minute TIMI 2 and 3 reperfusion rates on all randomly assigned patients with a technically adequate coronary angiogram. A 1-sided 95% confidence interval was used for the difference between the initial reperfusion rates of the enoxaparin-and UFH-treated patients in the intention-to-treat population. Noninferiority was to be accepted if the lower bound of the confidence interval did not exceed −10%. With a significance level set at 0.05 (1-sided), a power of 80% and an assumed patency rate of 80%, 198 patients per group were to be randomly assigned. A prespecified secondary analysis was performed in the subgroup (per protocol) whose initial angiogram was performed within the narrow time frame of 90 ±15 minutes of the start of treatment.

Reocclusion rates on repeat angiography (only performed if TIMI grade 2 or 3 flow was observed on the initial angiogram) were included as a secondary parameter. Reocclusion was defined either as a change from TIMI 3 and/or from TIMI 2 to TIMI 0 or 1. Angiographic data were analyzed by a core laboratory blinded to treatment assignment and clinical events.

Safety end points included the number of major hemorrhagic events. Safety end points were reviewed by a data safety monitoring board. Major hemorrhage was defined with the use of the TIMI criteria: a fall in hemoglobin levels ≥5 g/dL (not associated with CABG), intracranial hemorrhage, or cardiac tamponade. All suspected strokes were adjudicated by an independent neurology consultant.

Results

A total of 400 patients were enrolled in the study, 200 in each treatment arm from January 1999 through January 2000. Of
these patients, 380 had assessable angiographic data. Baseline characteristics were similar for the two treatment groups (Table 1). Partial thromboplastin times for patients randomly assigned to UFH, expressed as the ratio to control values in seconds, was measured at 6, 12, 24, 48, and 72 hours after the start of treatment. The median values at the specified time points were 2.2, 2.4, 2.7, 2.4, and 1.9 times the control value, respectively.

Patency rates (TIMI grades 2 and 3) of the infarct-related artery 90 minutes after start of therapy were 80.1% in patients treated with enoxaparin compared with 75.1% in the UFH group (Figure 2). The 5% absolute difference, arising mainly from a higher rate of TIMI 3 flow, represents a trend in favor of enoxaparin, confirming that enoxaparin was well within the criterion for noninferiority (10%), and approached that for superiority over UFH (lower bound of the 95% CI, 2.1%; see Figure 3). The noninferiority of enoxaparin when compared with UFH was confirmed in the per protocol population of 302 patients (lower bound of the 95% CI, 4.8%).

Two hundred fifty-nine patients with TIMI 2 or 3 flow on the initial angiogram and with an assessable angiogram at follow-up were assessed for reocclusion. Reocclusion, defined as deterioration from TIMI grade 2 or 3 at 90 minutes to grade 0 or 1 at follow-up, occurred in 5.9% and 9.8% of patients in the enoxaparin and UFH groups, respectively (Figure 4). Reocclusion of TIMI grade 3 arteries occurred in 3.1% and 9.1% of enoxaparin- and UFH-treated patients (P=0.12). If the rate of reocclusion is calculated over the per protocol population with assessable angiogram at follow-up, the rate of reocclusion from TIMI grade 3 flow to grade 0 or 1 was statistically significantly lower in the enoxaparin group (enoxaparin, 1.3%; UFH, 11.0%; P=0.02).

Safety
The treatment groups were similar with respect to safety end points (Table 2). Intracranial hemorrhage occurred in 2 patients (1%) in both groups. In-hospital TIMI major hemorrhage was seen in 3.6% of patients in the enoxaparin group compared with 3% receiving UFH. In-hospital fatality rates were 4.0% in the enoxaparin group versus 4.5% in the UFH group, and mortality rate at 30 days was 4.5% in the enoxaparin group and 5.0% in the UFH group.

Discussion
Adjunctive UFH used at the time of fibrin-selective fibrinolytic therapy for AMI improves early patency rates of the infarct-related artery.9,10 As a result of distinct pharmacologic and pharmacokinetic profiles of some LMWHs compared with UFH, they may offer benefits in this indication, but no previous early angiographic studies have directly compared the two classes of antithrombotic agents as adjuncts to thrombolysis in AMI. In the Fragmin in Acute Myocardial Infarction (FRAMI) study, subcutaneous dalteparin started 8 hours after thrombolysis with streptokinase in patients with acute anterior myocardial infarction provided a significant reduction in left ventricular thrombus formation 9 days after the acute event.24 However, this benefit was obtained at the expense of a higher bleeding risk (major hemorrhage: dalte-
parin 2.9% versus placebo 0.3%, \( P=0.006 \). In the recent placebo-controlled BIOchemical Markers in Acute Coronary Syndromes (BOMACS) II trial, dalteparin was investigated as an adjunct to thrombolysis with streptokinase and provided a nonsignificant trend toward increased TIMI grade 3 patency at 20 to 28 hours after randomization and noninvasive signs of early (90-minute) reperfusion.

The current randomized comparative study demonstrated that enoxaparin used immediately in conjunction with rt-PA was at least as effective as UFH in achieving infarct-related artery patency 90 minutes after the onset of treatment and exhibited a slight trend toward higher rates of recanalization, particularly in restoring TIMI grade 3 flow. Similarly, a trend was demonstrated for lower rates of reocclusion associated with enoxaparin compared with UFH (67% reduction in reocclusion from TIMI 3 flow).

These results with enoxaparin were achieved without an increase in adverse events, compared with UFH. The advantages of enoxaparin over UFH extend to practical benefits. The twice-daily, subcutaneous dosing schedule without monitoring of coagulation parameters represents a significant reduction in nursing time and laboratory costs compared with standard intravenous, dose-adjusted UFH, which is often difficult to achieve. Enoxaparin has been shown to be cost-saving when compared with UFH in the treatment of unstable angina and non–Q-wave myocardial infarction; however, it remains to be seen whether enoxaparin will be cost-effective when used as an adjunct to thrombolysis, and studies on a larger population are needed to investigate the pharmacoeconomics of enoxaparin in the clinical setting of AMI.

It should be noted that glycoprotein IIb/IIIa platelet receptor antagonists were not used in this trial to avoid a confounding variable. Nonetheless, treatment regimens combining enoxaparin with antiplatelet drugs more potent than aspirin are of interest and are now being investigated.

Current guidelines issued by the American College of Cardiology and American Heart Association for the acute treatment of patients with myocardial infarction recommend the adjunctive use of intravenous UFH in patients undergoing reperfusion therapy with thrombolytic agents. The guidelines advocate starting UFH at the initiation of thrombolytic therapy and continuing for 48 hours, or longer for patients at high risk of systemic or venous thromboembolism. The present study, should currently ongoing clinical studies confirm the safety of enoxaparin when used as an adjunct to fibrinolysis, suggests that this LMWH may be conveniently substituted for UFH in AMI.

### Appendix

The members of the Data Safety Monitoring Board were as follows: Pierre Théroux, MD (chair), Montreal Heart Institute, Montreal, Canada; Marcel van den Brand, MD, Academisch Ziekenhuis, Rotterdam, The Netherlands; David Sheps, MD, East Tennessee State University, Johnson City; Freek Verheugt, MD, University Hospital Nijmegen, Nijmegen, The Netherlands; Janet Wittes, PhD, Statistic Collaborative, Washington, DC.

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