Angiographic and Clinical Outcomes in Patients Receiving Low-Molecular-Weight Heparin Versus Unfractionated Heparin in ST-Elevation Myocardial Infarction Treated With Fibrinolytics in the CLARITY-TIMI 28 Trial

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Background—Low-molecular-weight heparin (LMWH) offers pharmacological and practical advantages over unfractionated heparin (UFH). Whether these advantages translate into greater infarct-related artery patency and fewer adverse clinical events in patients with ST-elevation myocardial infarction (STEMI) receiving fibrinolytic therapy remains under study.

Methods and Results—We compared angiographic and clinical outcomes in patients treated with LMWH (n=1429) versus UFH (n=1431) in CLARITY-TIMI 28, a randomized trial of clopidogrel versus placebo in STEMI patients aged 18 to 75 years undergoing fibrinolysis. After comprehensive adjustment for baseline characteristics, therapeutic interventions, and a propensity score, treatment with LMWH was associated with a significantly lower rate of a closed infarct-related artery or death or myocardial infarction before angiography (13.5% versus 22.5%, adjusted OR 0.76, P=0.027). Treatment with LMWH was also associated with a significantly lower rate of cardiovascular death or recurrent myocardial infarction through 30 days (6.9% versus 11.5%, adjusted OR 0.68, P=0.030). The lower event rates were observed in patients allocated to clopidogrel and in those who underwent percutaneous coronary intervention. Rates of TIMI major bleeding through 30 days (1.6% versus 2.2%, P=0.27) and intracranial hemorrhage (0.6% versus 0.8%, P=0.37) were similar in the LMWH and UFH groups. Patients who received both clopidogrel and LMWH, in addition to a standard fibrinolytic and aspirin, had a particularly high rate of infarct-related artery patency (90.9%) and particularly low rates of cardiovascular death (3.2%), recurrent myocardial infarction (3.0%), and major bleeding (1.8%).

Conclusions—In patients with STEMI receiving fibrinolytic therapy, use of LMWH with other standard therapies, including clopidogrel and aspirin, is associated with improved angiographic outcomes and lower rates of major adverse cardiovascular events. (Circulation. 2005;112:3846-3854.)

Key Words: myocardial infarction • heparin • fibrinolysis • angiography

Antithrombin therapy plays an important role in the pharmacological reperfusion of patients presenting with an ST-elevation myocardial infarction (STEMI). Unfractionated heparin (UFH) has been the traditional antithrombin used, but it has several well-documented pharmacological and practical limitations. More recently, low-molecular-weight heparin (LMWH) has been tested as an alternative to UFH. Recent clinical trials in patients with non–ST-elevation acute coronary syndromes have demonstrated the noninferiority of the LMWH enoxaparin compared with UFH.2,3

Clinical Perspective p 3854

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Several clinical trials have compared LMWH with UFH in patients with STEMI undergoing fibrinolytic therapy and have generally reported favorable effects with LMWH.\(^4\) However, since these trials were conducted, several other important therapeutic interventions in the care of patients with STEMI have been introduced, including dual antiplatelet therapy with aspirin plus clopidogrel\(^5\)\(^6\) and routine coronary angiography after fibrinolytic therapy.\(^7\) The angiographic and clinical efficacy, as well as the safety, of LMWH in the setting of these advances remains unknown.

The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–Thrombolysis in Myocardial Infarction (TIMI) 28 trial recently demonstrated the benefit of the addition of clopidogrel to standard fibrinolytic regimens in patients presenting with STEMI.\(^8\) Within this trial, patients received UFH or LMWH at the discretion of the treating physician. Per protocol, all patients were to undergo routine angiography 2 to 8 days after enrollment, with subsequent percutaneous coronary intervention (PCI) at the discretion of the treating physician. This design created the opportunity to compare the angiographic and clinical outcomes in patients receiving UFH versus LMWH in a prospective cohort of patients who received modern, protocol-guided treatment that included the use of routine angiography and who were randomized to clopidogrel or placebo.

**Methods**

**Patient Population and Procedures**

The design of CLARITY-TIMI 28 has been reported.\(^8\) In brief, 3491 patients 18 to 75 years of age presenting within 12 hours of onset of STEMI were randomized to clopidogrel (300-mg loading dose, then 75 mg once daily) or placebo in a double-blind fashion. Patients treated with clopidogrel within 7 days before enrollment or in whom treatment with clopidogrel or a glycoprotein (GP) IIb/IIIa inhibitor before angiography was planned, patients with cardiacogenic shock, patients who had undergone prior coronary artery bypass grafting, and patients with a serum creatinine >2.5 mg/dL were excluded. In addition, patients who weighed <67 kg and had received a >4000-U bolus or who weighed >67 kg and had received a >5000-U bolus of UFH and patients who had received enoxaparin >30 mg IV or >1.1 mg/kg SC, dalteparin >130 U/kg, or nadroparin >90 anti-Xa IU/kg within the preceding 8 hours were excluded.

All patients were to be treated with a standard fibrinolytic regimen that included a fibrinolytic (selected by the treating physician), aspirin (recommended dose of 150 to 325 mg on the first day and 75 to 162 mg daily thereafter), and heparin for 48 hours (use of heparin in patients receiving streptokinase was at the discretion of the treating physician). The recommended UFH dosing was 60 U/kg IV bolus (maximum 4000 U) followed by an infusion at 12 U · kg\(^{-1}\) · h\(^{-1}\) (maximum 1000 U/h).\(^9\) The recommended enoxaparin dosing was an initial 30-mg IV bolus, immediately followed by the first subcutaneous dose of 1 mg/kg, and then additional subcutaneous doses of 1 mg/kg every 12 hours thereafter (with the first 2 subcutaneous doses not to exceed 100 mg). The recommended dalteparin dosing was either a 30-IU/kg IV bolus immediately, followed by a first subcutaneous dose of 90 IU/kg and then additional subcutaneous doses of 120 IU/kg every 12 hours thereafter, or an initial 100-IU/kg subcutaneous dose and then subcutaneous doses of 120 IU/kg every 12 hours thereafter. The recommended nadroparin dosing was an initial 86–anti-Xa IU/kg IV dose, and then 86–anti-Xa IU/kg subcutaneous doses every 12 hours thereafter. Patients who received more than 1 type of heparin were categorized on the basis of the predominant heparin they received, which was prospectively defined as the type of heparin the patients received for the majority of time while awaiting angiography. Patients who did not receive a fibrinolytic or did not receive heparin were excluded from these analyses.

Per protocol, all patients were to undergo coronary angiography 48 to 192 hours after randomization to determine patency of the infarct-related artery. Patients were followed up for clinical outcomes and adverse events during their index hospitalization. Telephone follow-up was performed at 30 days after randomization to assess for clinical outcomes or adverse events, which were verified with medical records. Follow-up was complete in 99.98% of patients.

The main study protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients.

**Outcomes**

The primary efficacy outcomes for this analysis were the composite of an occluded infarct-related artery, or death or recurrent myocardial infarction (MI) before angiography or by day 8 or hospital discharge for patients who did not undergo angiography (the primary end point in CLARITY-TIMI 28), and cardiovascular death or recurrent MI from randomization to 30 days. An occluded infarct-related artery was defined as TIMI flow grade 0 or 1 on the diagnostic angio gram as determined in a blinded fashion by the TIMI Angiographic Core Laboratory. The definition of recurrent MI has been described previously.\(^9\) Additional angiographic outcomes included TIMI flow grade 3, TIMI myocardial perfusion grade 2/3, and the presence of intra coronary thrombus. Additional clinical outcomes included stroke through 30 days and the composite of cardiovascular death, recurrent MI, or stroke. The primary safety outcome for this analysis was the rate of TIMI major bleeding through 30 days.\(^10\) Other safety outcomes included intracranial hemorrhage and TIMI minor bleeding. All ischemic and any clinically significant bleeding events were adjudicated by an independent Clinical Events Committee that was blinded to treatment assignment.

**Statistical Analysis**

The characteristics of patients who were treated by their physician with LMWH versus those treated with UFH were compared with t tests for normally distributed continuous variables, Wilcoxon rank sum tests for nonnormally distributed continuous variables, and \(\chi^2\) tests for categorical variables. Efficacy outcome analyses were performed with a logistic regression model that included terms for type of heparin, type of fibrinolytic, infarct location, study medication, statin use, ACE inhibitor or angiotensin receptor blocker use, history of hypertension, time to angiography, and a propensity score for LMWH use. A propensity score allows for adjustment for potential selection bias when comparing the effect of nonrandomized treatments.\(^11\)\(^12\) The propensity score was constructed by application of a forward selection algorithm with an inclusion probability value threshold of <0.10 to a logistic regression model that predicted LMWH use and contained candidate baseline variables that included demographics, country, traditional cardiovascular risk factors, prior cardiac disease and procedures, cardiac medications, time to presentation, initial vital signs, infarct location, and type of lytic. The final propensity score included terms for country, race, type of fibrinolytic, and infarct location. Incidences of safety outcomes were compared with Fisher’s exact test.

Three other studies of patients with STEMI receiving fibrinolytic therapy have compared rates of infarct-related artery patency in patients receiving LMWH versus UFH (second trial of Heparin and Aspirin Reperfusion Therapy [HART II],\(^13\) Assessment of the Safety and Efficacy of a New Thrombolytic Regimen [ASSENT] Plus,\(^14\) and ENTIRE-TIMI 23 [Enoxaparin and TNK-PA With or Without GP IIb/IIIa Inhibitor as Reperfusion Strategy in STEMI–TIMI 23])\(^15\). Because CLARITY-TIMI 28 and each of these other studies evaluated patency at a different time point after initiation of fibrinolytic therapy, summary data on the rates of infarct-related artery patency were abstracted from the other publications, and meta-regression with a random-effects model and unrestricted maximum-likelihood estimates for between-trial variance was used.
Analyses were done with Stata/SE version 8.2 (StataCorp) and Comprehensive Meta Analysis version 2.2.021 (Biostat).

Results

Overall, 1431 patients were treated with UFH and 1429 were treated with LMWH as their predominant anticoagulation in CLARITY-TIMI 28. For patients who weighed ≤67 kg, the mean bolus of UFH was 4129 ± 767 U (69 ± 13 U/kg), and the mean initial infusion rate was 841 ± 176 U/h (14 ± 3 U · kg⁻¹ · h⁻¹). For patients who weighed >67 kg, the mean bolus was 4518 ± 844 U (54 ± 12 U/kg), and the mean initial infusion rate was 978 ± 151 U/h (12 ± 2 U · kg⁻¹ · h⁻¹). The mean activated partial thromboplastin time after the bolus was 58 ± 29 seconds. The median duration of the UFH infusion was 48 hours (interquartile range 23 to 65 hours). Of the patients who received LMWH, 85% received enoxaparin, and the remaining 15% received nadroparin, dalteparin, tinzaparin, or certoparin.

Of the patients treated with enoxaparin, 624 (51%) received an initial 30-mg IV bolus, and the median maintenance dose was 1.0 mg/kg SC twice daily (interquartile range 0.9 to 1.0 mg/kg). The median number of doses of LMWH given was 7 (interquartile range 5 to 11).

The 2 groups were well balanced with regard to baseline characteristics (Table 1) and cardiac medications (Table 2). Approximately 80% of patients received a fibrin-specific lytic, and the remainder received streptokinase. Ninety-eight percent of patients received aspirin and, as expected from randomization, half of patients were allocated to clopidogrel study medication. Ninety-five percent of patients underwent angiography, and the median time to angiography was 2.9 (0.8 to 4.6) days among patients receiving UFH and 3.8 (2.6 to 5.4) days among patients receiving LMWH (p<0.001). Patients receiving LMWH were less likely to undergo PCI (p<0.001), less likely to require urgent revascularization (p<0.001), and less likely to be treated with a GP IIb/IIIa inhibitor (p<0.001).

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LMWH (n=1429)</th>
<th>UFH (n=1431)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 y</td>
<td>58±10</td>
<td>58±10</td>
<td>0.81</td>
</tr>
<tr>
<td>Male sex</td>
<td>422 (30)</td>
<td>437 (31)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypertension</td>
<td>563 (40)</td>
<td>616 (44)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>490 (39)</td>
<td>474 (39)</td>
<td>0.78</td>
</tr>
<tr>
<td>Current smoker</td>
<td>720 (51)</td>
<td>709 (50)</td>
<td>0.64</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>235 (17)</td>
<td>227 (16)</td>
<td>0.69</td>
</tr>
<tr>
<td>Prior MI</td>
<td>132 (9)</td>
<td>132 (9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>559 (39)</td>
<td>604 (42)</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135±23</td>
<td>135±22</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74±18</td>
<td>75±17</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD for normally distributed continuous variables and n (%) for dichotomous variables. Denominators are based on available data for each characteristic.

Table 2: Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LMWH (n=1429)</th>
<th>UFH (n=1431)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial pharmacological therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinolytic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrin-specific</td>
<td>1181 (83)</td>
<td>1134 (79)</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-fibrin-specific</td>
<td>248 (17)</td>
<td>297 (21)</td>
<td></td>
</tr>
<tr>
<td>Time from symptom onset to start of fibrinolytic, h</td>
<td>2.4 (1.7–3.9)</td>
<td>2.6 (1.7–3.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1409 (99)</td>
<td>1408 (98)</td>
<td>0.65</td>
</tr>
<tr>
<td>Clopidogrel (study drug)</td>
<td>729 (51)</td>
<td>709 (50)</td>
<td>0.43</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>1278 (89)</td>
<td>1273 (89)</td>
<td>0.69</td>
</tr>
<tr>
<td>Statin</td>
<td>1201 (84)</td>
<td>1150 (80)</td>
<td>0.01</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>993 (69)</td>
<td>1041 (73)</td>
<td>0.06</td>
</tr>
<tr>
<td>Coronary interventions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>1365 (95.5)</td>
<td>1347 (94.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Time from randomization to angiography, d</td>
<td>3.8 (2.6–5.4)</td>
<td>2.9 (0.8–4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI during index hospitalization</td>
<td>789 (55)</td>
<td>888 (62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent PCI</td>
<td>224 (16)</td>
<td>434 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent</td>
<td>758 (96)</td>
<td>837 (94)</td>
<td>0.09</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor use during PCI</td>
<td>223 (16)</td>
<td>306 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>59 (4)</td>
<td>65 (5)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

ARB indicates angiotensin receptor blocker.

Data are presented as n (%) for dichotomous variables and median (interquartile range) for continuous variables. Denominators are based on available data for each characteristic.
Angiographic Outcomes

Compared with patients receiving UFH, patients receiving LMWH had a lower rate of an occluded infarct-related artery or death or recurrent MI before angiography (13.5% versus 22.5%; Table 3). In a multivariable model that adjusted for baseline characteristics, infarct location, type of fibrinolytic, other cardiac medications, time to angiography, and a propensity score for LMWH use, LMWH remained significantly associated with a lower likelihood of an occluded infarct-related artery or death or recurrent MI before angiography (adjusted OR 0.76, 95% CI 0.60 to 0.97, P=0.027). The benefit associated with LMWH was directionally consistent among the components of the composite end point, with the adjusted ORs for an occluded infarct-related artery (0.78, 95% CI 0.61 to 1.01) and death or MI before angiography (0.58, 95% CI 0.34 to 0.98) both favoring use of LMWH. Patients receiving LMWH also had significantly higher rates of achieving TIMI flow grade 3 (69.9% versus 59.8%, adjusted OR 1.18, 95% CI 0.98–1.38, P=0.075) and a lower rate of intracoronary thrombus (23.4% versus 30.0%, adjusted OR 0.83, 95% CI 0.68–1.01, P=0.066).

The lower rate of an occluded infarct-related artery or death or recurrent MI before angiography associated with use of LMWH was consistent regardless of patient age, gender, infarct location, time from symptom onset to lytic administration, type of fibrinolytic, or clopidogrel use (Figure 1). Patients who received both clopidogrel and LMWH had an infarct-related artery patency rate of 90.9% and a TIMI flow grade 3 rate of 73.2%.

In addition to CLARITY-TIMI 28, 3 other studies have compared the rate of infarct-related artery patency associated with LMWH versus UFH in patients with STEMI receiving fibrinolytic therapy. The absolute difference in patency rates between patients receiving LMWH versus UFH is plotted against the time of assessment of patency in Figure 2. Meta-regression demonstrated that the magnitude of the observed benefit in infarct-related artery patency in those treated with LMWH versus UFH was greater the later the assessment of patency, with the absolute benefit growing by 1.5% (95% CI 0.3% to 3.2%, P=0.09) for every 24 hours from initiation of reperfusion therapy.

Clinical Outcomes

By 30 days, treatment with LMWH was associated with a significantly lower rate of cardiovascular death or recurrent MI (6.9% versus 11.5%, adjusted OR 0.68, 95% CI 0.48 to 0.96, P=0.030). The majority of benefit was related to the lower rate of recurrent MI (3.8% versus 7.1%, adjusted OR 0.62, 95% CI 0.42 to 0.92), with a more modest difference in cardiovascular mortality (3.1% versus 4.8%, adjusted OR 0.83, 95% CI 0.42 to 1.64). Treatment with LMWH was also associated with a numerically lower rate of stroke (1.3% versus 1.5%, adjusted OR 0.74, 95% CI 0.26 to 2.12), with a significantly lower rate of the triple composite end point of cardiovascular death, recurrent MI, or stroke (7.6% versus 12.6%, adjusted OR 0.66, 95% CI 0.47 to 0.93, P=0.017).

The association between LMWH use and lower rates of major adverse cardiovascular events was consistent regardless of patient age, gender, infarct location, or clopidogrel use. Of note, patients who received both clopidogrel and LMWH, in addition to a standard fibrinolytic and aspirin, had particularly low rates of cardiovascular death (3.2%) and recurrent MI (3.0%). Although not a baseline characteristic, among patients who subsequently underwent PCI, treatment with LMWH was also associated with a lower rate of cardiovascular death or MI (adjusted OR 0.60, 95% CI 0.40 to 0.91). As a sensitivity analysis to explore any time dependence of the apparent clinical benefit, we examined the association between LMWH use and the incidence of cardiovascular death or MI in the first 48 hours (the duration of anticoagulant therapy recommended in the protocol), and found that the lower risk associated with LMWH use was already evident at this early time.
point (3.6% versus 7.9%, adjusted OR 0.60, 95% CI 0.36 to 0.99, P=0.047).

Safety
There was no significant excess in the rates of TIMI major bleeding (1.6% versus 2.2%), TIMI minor bleeding (1.3% versus 1.2%), or intracranial hemorrhage (0.6% versus 0.8%) in patients who received LMWH compared with those who received UFH (Table 5). The rates of TIMI major bleeding in patients receiving LMWH did not differ from those receiving UFH in patients receiving clopidogrel (1.8% versus 1.9%), patients undergoing PCI during the index hospitalization (0.8% versus 1.7%), patients receiving a GP IIb/IIIa inhibitor (2.7% versus 1.6%), or patients with an estimated glomerular filtration rate <60 mL·min⁻¹·1.73 m⁻² (2.6% versus 2.7%; all P values nonsignificant).

Discussion
The present study demonstrates that among patients with STEMI receiving fibrinolytic therapy, treatment with LMWH compared with UFH was associated with improved reperfusion and a lower rate of cardiovascular death and recurrent MI. Importantly, the benefit associated with use of LMWH was seen in patients who received clopidogrel on presentation and in those who underwent PCI. There was no significant excess in rates of TIMI major or minor bleeding or intracranial hemorrhage.

LMWH has several pharmacodynamic and pharmacokinetic advantages over UFH. Specifically, compared with UFH, LMWH inhibits the coagulation cascade more proximally owing to a higher ratio of anti-Xa to anti-IIa activity, more fully suppresses the rise of von Willebrand factor, is more resistant to inactivation by platelet factor 4, and is less likely to trigger heparin-induced thrombocytopenia. LMWH also has higher and more consistent bioavailability after subcutaneous injection, has a longer half-life, and is bound less readily by acute phase reactants and vascular endothelial cells. These properties lead to a more predictable anticoagulation effect without the need for laboratory monitoring, although the lack of a point-of-care assay to measure the anticoagulant effect of LMWH has been a barrier to the widespread adoption of LMWH in the cardiac catheterization laboratory.

LMWH has been compared with UFH in the context of fibrinolytic therapy for STEMI in 3 phase II angiographic studies and 2 larger randomized clinical trials. In the 3 angiographic trials, LMWH resulted in a nonsignificant trend toward improved early patency in 1 trial (HART II), no difference in early patency in another trial (ENTIRE-
TIMI 23), and a higher rate of late patency but not TIMI flow grade 3 in the third trial (ASSENT Plus).\textsuperscript{13–15} However, ENTIRE-TIMI 23 did demonstrate a statistically significant reduction in the rate of death or MI with enoxaparin (4.4% versus 15.9%, \( P \leq 0.005 \)).\textsuperscript{15} The largest randomized trial completed to date comparing LMWH with UFH is ASSENT-3, which demonstrated that LMWH significantly reduced the risk of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia by 26%.\textsuperscript{23} The subsequent ASSENT-3 Plus trial compared prehospital therapy with tenecteplase and either LMWH or UFH and found a trend toward an 18% lower rate of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia.\textsuperscript{24} However, mortality itself trended in the opposite direction, with higher rates in those treated with LMWH.

The results of the present study build on these prior studies in several important ways. First, the present data represent the largest angiographic study of LMWH versus UFH in STEMI. We demonstrate that use of LMWH is associated with a significantly higher rate of achieving optimal TIMI flow in the infarct-related artery several days after fibrinolysis than is seen with use of UFH. Moreover, we found strong trends toward higher rates of optimal myocardial perfusion and lower rates of intracoronary thrombus. Second, using data from all of the available angiographic studies, we found that the magnitude of the absolute difference in the rates of infarct-related artery patency achieved with LMWH versus UFH appeared to be greater the later the time of assessment. This finding may reflect the more stable anticoagulant effect of LMWH having a greater effect on preventing reocclusion than on facilitating initial reperfusion.\textsuperscript{13,25,26} Third, we show that treatment with LMWH was associated with a significantly lower rate of cardiovascular death or recurrent MI over 30 days. This observation was in the setting of UFH being administered in close adherence to the most recent American College of Cardiology/American Heart Association guidelines, with an emphasis on weight-based dosing and early monitoring of activated partial thromboplastin time values.\textsuperscript{9} ExTRACT-TIMI 25, a large phase III clinical trial that is examining the clinical efficacy of LMWH versus UFH in more than 20 000 patients with STEMI, should, when completed, provide definitive data.\textsuperscript{27} Fourth, we evaluated LMWH in the setting of modern pharmacological reperfusion for STEMI with routine angiography, demonstrating a preserved benefit even in patients receiving clopidogrel and in those undergoing PCI. Although there are no randomized trials of LMWH versus UFH in the setting of PCI for STEMI, the recently presented results of STEEPLE (Safety and Efficacy of Enoxaparin in Elective Percutaneous Coronary Intervention) demonstrate that in elective PCI, enoxaparin appears to be as effective as and safer than UFH.\textsuperscript{28} Fifth, we add data on the safety
of LMWH, showing there is no excess in TIMI major bleeding or intracranial hemorrhage, even when LMWH is combined with clopidogrel or given in the setting of angiography or PCI, with GP IIb/IIIa use, or in patients with moderately impaired renal function.

Potential limitations of the present study merit consideration. Treatment with LMWH versus UFH was not randomized but rather was given at the discretion of the treating physician, and therefore the relationship between anticoagulant and outcomes could be influenced by patient or physician factors associated with the choice of anticoagulant. However, we conducted a comprehensive search for potential confounders, generated a propensity score for LMWH use, and included that score and other important prognostic and treatment-related variables in our multivariable analyses to minimize any residual confounding. The treatment duration differed between those receiving LMWH and those receiving UFH; however, this difference should have had a minimal impact, because we adjusted for time to angiography in our analyses, and a significant clinical difference in the rates of cardiovascular death or MI was evident within the first 48 hours. CLARITY-TIMI 28 enrolled patients ≤75 years of age and with a serum creatinine ≤2.5 mg/dL. Thus, we cannot comment on the efficacy and safety of LMWH in elderly patients or in those with severe renal insufficiency. The net clinical benefit of combined antithrombotic pharmacotherapies in an older, higher-risk population requires additional study.

In conclusion, we found that in patients 18 to 75 years of age with STEMI treated with fibrinolytic therapy, treatment with LMWH, compared with UFH, is associated with improved late patency and a lower rate of cardiovascular death or recurrent MI, without a significant increase in major or minor bleeding. Moreover, the favorable efficacy and safety profile associated with use of LMWH was observed in patients receiving dual antiplatelet therapy with aspirin plus clopidogrel and in patients undergoing

### TABLE 4. Clinical Outcomes Through 30 Days

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LMWH (n=1429)</th>
<th>UFH (n=1431)</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or recurrent MI</td>
<td>98 (6.9)</td>
<td>165 (11.5)</td>
<td>0.68 (0.48–0.96)</td>
<td>0.030</td>
</tr>
<tr>
<td>CV death, recurrent MI, or stroke</td>
<td>109 (7.6)</td>
<td>180 (12.6)</td>
<td>0.66 (0.47–0.93)</td>
<td>0.017</td>
</tr>
<tr>
<td>CV death</td>
<td>44 (3.1)</td>
<td>68 (4.8)</td>
<td>0.83 (0.42–1.64)</td>
<td>0.584</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>54 (3.8)</td>
<td>101 (7.6)</td>
<td>0.62 (0.42–0.92)</td>
<td>0.017</td>
</tr>
<tr>
<td>Stroke</td>
<td>18 (1.3)</td>
<td>22 (1.5)</td>
<td>0.74 (0.26–2.12)</td>
<td>0.580</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular.

Multivariable logistic regression model included terms for type of heparin, type of fibrinolytic, infarct location, study medication, statin use, ACE inhibitor or angiotensin receptor blocker use, history of hypertension, time to angiography, and a propensity score for LMWH use.

### TABLE 5. Safety Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>LMWH (n=1429)</th>
<th>UFH (n=1431)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>23 (1.6)</td>
<td>31 (2.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>In those treated with clopidogrel</td>
<td>13/727 (1.8)</td>
<td>13/696 (1.9)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>In those undergoing PCI</td>
<td>6/789 (0.8)</td>
<td>5/888 (1.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>In those treated with a GP IIb/IIIa inhibitor</td>
<td>6/223 (2.7)</td>
<td>5/306 (1.6)</td>
<td>0.54</td>
</tr>
<tr>
<td>In those with estimated GFR &lt;60 mL·min⁻¹·1.73 m⁻²</td>
<td>5/194 (2.6)</td>
<td>6/223 (2.7)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>18 (1.3)</td>
<td>17 (1.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>In those treated with clopidogrel</td>
<td>13/727 (1.8)</td>
<td>8/696 (1.2)</td>
<td>0.38</td>
</tr>
<tr>
<td>In those undergoing PCI</td>
<td>12/789 (1.5)</td>
<td>11/888 (1.2)</td>
<td>0.68</td>
</tr>
<tr>
<td>In those treated with a GP IIb/IIIa inhibitor</td>
<td>4/223 (1.8)</td>
<td>7/306 (2.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>In those with estimated GFR &lt;60 mL·min⁻¹·1.73 m⁻²</td>
<td>4/194 (2.1)</td>
<td>6/223 (2.7)</td>
<td>0.76</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>8 (0.6)</td>
<td>12 (0.8)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate.

Data are presented as n (%); for subgroups, denominators are also provided. Bleeding events were categorized according to TIMI criteria.
PCI. The combination of a fibrinolytic, aspirin, clopidogrel, and LMWH, followed by routine angiography within several days, thus offers an attractive reperfusion strategy for patients with STEMI.

**Disclosures**

Drs Sabatine, Dellborg, Keltai, Gibson, Cannon, and Braunwald and Carolyn McCabe report having received research grant support and/or honoraria from and/or served on scientific advisory boards for Bristol-Myers Squibb; Drs Sabatine, Morrow, Montalescot, Dellborg, Keltai, Gibson, Cannon, Antman, and Braunwald and Carolyn McCabe report having received research grant support and/or honoraria from and/or served on scientific advisory boards for Sanofi-Aventis. Dr Cannon reports having received research grant support and/or honoraria from and/or served on scientific advisory boards for AstraZeneca, Glaxo-SmithKline, Guilford Pharmaceuticals, Merck, Merck–Scheringer Plough, Millennium, Pfizer, and Schering-Plough. Carolyn McCabe and Dr Braunwald report having received research grant support from Eli Lilly.

**References**

CLINICAL PERSPECTIVE

We compared angiographic and clinical outcomes in patients treated with low-molecular-weight heparin (LMWH) versus unfractionated heparin (UFH) in CLARITY-TIMI 28, a randomized trial of clopidogrel versus placebo in ST-elevation myocardial infarction (STEMI) treated with fibrinolytics in which all patients were to undergo angiography after 48 hours. We found that LMWH was associated with 24% lower odds of a closed infarct-related artery or death or myocardial infarction before angiography. Using data from all of the available angiographic studies, we found that the magnitude of the absolute difference in the rates of infarct-related artery patency achieved with LMWH versus UFH appeared to be greater the later the time of assessment, potentially reflecting the more stable anticoagulant effect of LMWH having a greater effect on preventing reocclusion than on facilitating initial reperfusion. We also found that LMWH was associated with 32% lower odds of cardiovascular death or recurrent myocardial infarction through 30 days. LMWH appeared to be safe, with no excess in TIMI major bleeding or intracranial hemorrhage. Patients who received both clopidogrel and LMWH, in addition to a standard fibrinolytic and aspirin, had a particularly high rate of infarct-related artery patency (90.9%) and particularly low rates of cardiovascular death (3.2%) or recurrent myocardial infarction (3.0%). While we await the results of ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment Thrombolysis in Myocardial Infarction-Study 25), a very large randomized trial of LMWH versus UFH in STEMI, the combination of a fibrinolytic, aspirin, clopidogrel, and LMWH, followed by routine angiography within several days, offers an attractive reperfusion strategy for patients with STEMI.
Angiographic and Clinical Outcomes in Patients Receiving Low-Molecular-Weight Heparin Versus Unfractionated Heparin in ST-Elevation Myocardial Infarction Treated With Fibrinolytics in the CLARITY-TIMI 28 Trial
Marc S. Sabatine, David A. Morrow, Gilles Montalescot, Mikael Dellborg, Jose L. Leiva-Pons, Matyas Keltai, Sabina A. Murphy, Carolyn H. McCabe, C. Michael Gibson, Christopher P. Cannon, Elliott M. Antman and Eugene Braunwald
for the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators

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