Unfractionated and Low-Molecular-Weight Heparin as Adjuncts to Thrombolysis in Aspirin-Treated Patients With ST-Elevation Acute Myocardial Infarction
A Meta-Analysis of the Randomized Trials

John W. Eikelboom, MBBS*; Daniel J. Quinlan, MBBS*; Shamir R. Mehta, MD; Alexander G. Turpie, MD; Ian B. Menown, MD; Salim Yusuf, DPhil

Background—There is uncertainty about the role of intravenous unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) in patients with ST-elevation myocardial infarction (STEMI) treated with aspirin and thrombolysis.

Methods and Results—We performed a meta-analysis of the randomized trials to assess the effect of UFH and LMWH on reinfarction, death, stroke, and bleeding. Fourteen trials involving a total of 25,280 patients were included (1239 comparing intravenous UFH versus placebo or no heparin; 16,943 comparing LMWH versus placebo; and 7098 comparing LMWH versus intravenous UFH). Intravenous UFH during hospitalization did not reduce reinfarction (3.5% versus 3.3%; odds ratio [OR], 1.08; 95% CI, 0.58 to 1.99) and did not increase major bleeding (4.2% versus 3.4%; OR, 1.21; 95% CI, 0.67 to 2.18) but increased minor bleeding (19.6% versus 12.5%; OR, 1.72; 95% CI, 1.22 to 2.43). During hospitalization/at 7 days, LMWH compared with placebo reduced the risk of reinfarction by approximately one quarter (1.6% versus 2.2%; OR, 0.72; 95% CI, 0.58 to 0.90; number needed to treat [NNT] = 167) and death by ≈10% (7.8% versus 8.7%; OR, 0.90; 95% CI, 0.80 to 0.99; NNT = 111) but increased major bleeding (1.1% versus 0.4%; OR, 2.70; 95% CI, 1.83 to 3.99; number needed to harm [NNH] = 143) and intracranial bleeding (0.3% versus 0.1%; OR, 2.18; 95% CI, 1.07 to 4.52; NNH = 500). The reduction in death with LMWH remained evident at 30 days. LMWH compared with UFH during hospitalization/at 7 days reduced reinfarction by ≈45% (3.0% versus 5.2%; OR, 0.57; 95% CI, 0.45 to 0.73; NNT = 45), did not reduce death (4.8% versus 5.3%; OR, 0.92; 95% CI, 0.74 to 1.13) or increase major bleeding (3.3% versus 2.5%; OR, 1.30; 95% CI, 0.98 to 1.72), but increased minor bleeding (22.8% vs 19.4%; OR, 1.26; 95% CI, 1.12 to 1.43). The reduction in reinfarction remained evident at 30 days.

Conclusions—In aspirin-treated patients with STEMI who are treated with thrombolysis, intravenous UFH has not been shown to prevent reinfarction or death. LMWH given for 4 to 8 days compared with placebo reduces reinfarction by approximately one quarter and death by ≈10% and when directly compared with UFH reduces reinfarction by almost one half. These data suggest that LMWH should be the preferred antithrombin in this setting. (Circulation. 2005;112: 3855-3867.)

Key Words: heparin ■ meta-analysis ■ myocardial infarction ■ thrombolysis

Thrombus formation at the site of rupture of vulnerable atherosclerotic plaque in a coronary artery is the most common underlying cause of acute coronary syndrome.1,2 Patients without persistent ST-elevation on the presenting ECG usually have transient or incomplete thrombotic occlusion of the culprit coronary artery, and their risk of reinfarction is significantly reduced by treatment with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) in combination with aspirin.3-4 By contrast, patients with ST-elevation myocardial infarction (STEMI) usually have complete thrombotic occlusion of the culprit coronary artery. Aspirin and thrombolytic therapy reduce reinfarction and death,5,6 but the role of anticoagulation remains unclear. Intravenous UFH is commonly recommended in those patients treated with a fibrin-specific thrombolytic agent or at high risk of systemic emboli5,6 but has not been shown in

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individual trials to reduce reinfarction or death and may increase bleeding.7–10 A recently completed large phase 3 trial demonstrated that LMWH (reviparin) reduces reinfarction and death,11 but it is unclear from direct randomized comparisons whether LMWH is superior to UFH.12,13

To further clarify the efficacy and safety of UFH and LMWH for the treatment of STEMI, we performed a meta-analysis of randomized trials comparing UFH or LMWH with untreated control (no heparin) or placebo or comparing UFH with LMWH in patients routinely treated with aspirin and a thrombolytic agent. We did not include trials that evaluated the use of subcutaneous UFH because this is not recommended in the treatment of STEMI and has not undergone further randomized evaluation since it was last reviewed.9

Methods
A protocol was prospectively developed, detailing the objectives, criteria for study selection, approach to assessing study quality, primary and secondary outcomes, and statistical methodology.

Study Identification
We identified relevant published and unpublished unconfounded randomized trials that compared intravenous UFH or subcutaneous LMWH with untreated control or placebo or compared intravenous UFH with subcutaneous LMWH for the treatment of STEMI. We searched electronic databases (MEDLINE and EMBASE) from January 1966 to February 2005 and the Cochrane Library (2005, Issue 1) using the terms acute myocardial infarction, ST elevation, randomized controlled trial, controlled clinical trial, and random, in combination with generic and trade names of individual LMWH preparations and thrombolytic agents. Bibliographies of journal articles were hand-searched to locate additional studies, and abstracts from major international cardiology meetings (American College of Cardiology [ACC], American Heart Association [AHA], and European Society of Cardiology [ESC]) held during the last 5 years were reviewed. Relevance was assessed with the use of a hierarchical approach based on title, abstract, and the published manuscript.

Study Selection
Two investigators (J.W.E., D.J.Q.) independently evaluated studies for possible inclusion, and any disagreements were resolved by discussion. To be included, studies had to (1) be properly randomized; (2) include patients with STEMI treated with aspirin and thrombolysis; (3) compare intravenous UFH or LMWH with placebo or untreated control or compare intravenous UFH with LMWH; and (4) report reinfarction or death as outcomes.

Assessment of Study Quality
We modified the study quality criteria outlined by Schulz and colleagues14 to evaluate the studies included in our meta-analysis. These criteria include (1) proper concealment of the allocation sequence; (2) blinding of the patient and the investigator assessing clinical outcomes to treatment allocation; and (3) completeness of follow-up.

Data Extraction
Two investigators (J.W.E., D.J.Q.) independently extracted data on study design, study quality, and the following efficacy and safety outcomes in-hospital or at approximately day 7 and at approximately day 30: (1) myocardial infarction (reinfarction); (2) stroke (ischemic, hemorrhagic); (3) death; (4) minor bleeding; and (5) major bleeding. We accepted the authors’ definitions for clinical outcomes and did not attempt to reclassify them retrospectively. The data abstracted for each trial were confirmed by reviewer consensus and then sent to the first or corresponding author for verification. Missing data were requested from the authors or sponsoring pharmaceutical company.

Statistical Analysis
We used a fixed-effects model based on the Mantel-Haenszel method for combining results from the individual trials.15 We calculated the odds ratio (OR) and 95% CI. The test of heterogeneity was calculated by the Mantel-Haenszel method. All statistical calculations were performed with the use of Comprehensive Meta Analysis, version 1.0.23 (Biostat).

Subgroup analyses were planned to explore the effect of (1) different LMWH preparations and (2) UFH or LMWH when used with non–fibrin-specific versus fibrin-specific thrombolytic agents. Sensitivity analyses were conducted to further explore the robustness of our results. To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we deleted studies one at a time. An inverted funnel plot of treatment effect versus study precision was created for the primary outcome to look for possible publication bias,16 a technique that may be helpful to determine whether additional small studies may have been conducted but not published because of unfavorable or negative results. We also compared results obtained with a fixed effects model with those obtained with a random effects model.

Results

Study Selection
The process of study selection is outlined in Figure 1. Our search yielded 1278 citations. After their titles were scanned, 39 potentially eligible studies remained. After review of abstracts, an additional 16 studies were excluded.17–32 After review of the full article, an additional 8 studies were excluded because they were not properly randomized (n=3)33–35, because at least 1 randomized treatment group did not receive aspirin (n=3)36–38, or because they were preliminary reports or the results of a substudy with the main results having been reported elsewhere (n=2).39,40 Clinical outcome data could not be obtained for 1 additional study,41 leaving 14 randomized trials, involving a combined total of 25280 patients, for inclusion in the meta-analysis (Tables 1 to 3).11,42–54

UFH Versus Control (4 Trials; n=1239)

Designs of Included Studies
Table 1 summarizes the study designs.42–45 Two studies used streptokinase,42,44 1 alteplase,43 and 1 anistreplase.44 The initial dose of aspirin was at least 200 mg in all the trials and was followed by a maintenance dose of between 75 and 325 mg/d. The duration of UFH treatment was between 1 and 5 days.

Study Quality
No information was provided on the methods used to generate the randomized treatment allocation in any of the 4 included studies. Concealment of treatment allocation appeared adequate in the 3 studies that reported this.42,43,45 Two of the 4 studies were double-blind and placebo controlled,43,44 and follow-up was complete in the 1 study that reported this.42

Outcomes
Reinfarction, Stroke, Death
Neither the individual randomized trials nor their pooled results showed a significant reduction in reinfarction or death with UFH compared with no heparin or placebo (Table 4, Figure 2). There was a modest nonsignificant excess of

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strokes in patients treated with UFH (11 events [1.8%] versus 4 events [0.7%]), which was largely accounted for by an increase in intracranial hemorrhage (5 events [0.8%] versus 1 event [0.2%]).

**Bleeding**

There was a significant excess of minor bleeding (101 events [19.6%] versus 63 events [12.5%]; OR, 1.72; 95% CI, 1.22 to 2.43) and a similar pattern of increased major bleeding (26

**TABLE 1. UFH vs no Heparin or Placebo: Trial Design**

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>N</th>
<th>Blinding</th>
<th>Thrombolysis</th>
<th>Randomized Treatment</th>
<th>Primary Outcome</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-2 Pilot, 1987</td>
<td>Suspected MI &lt;24 h</td>
<td>200</td>
<td>Open label</td>
<td>SK 1.5 MU over 1 h</td>
<td>UFH* No bolus, 1000 IU/h for 48 h†</td>
<td>No heparin 325 mg/d</td>
<td>New MI, death In-hospital, 1 y (death)</td>
</tr>
<tr>
<td>ECSG, 1992</td>
<td>Age 21–70 y; STEMI, ≤6 h</td>
<td>652</td>
<td>Double-blind</td>
<td>tPA 100 mg over 3 h</td>
<td>Control 300 mg PO or 250 mg IV‡; Placebo</td>
<td>75–125 mg PO Alternate days</td>
<td>Angiographic patency In-hospital</td>
</tr>
<tr>
<td>OSIRIS, 1992</td>
<td>STEMI, ≤6 h</td>
<td>128</td>
<td>Double-blind</td>
<td>SK 1.5 MU over 1 h</td>
<td>Placebo 10 000 IU bolus, 1000 IU/h for 24 h</td>
<td>200 mg/d</td>
<td>Reperfusion, angiographic patency, LVEF In-hospital</td>
</tr>
<tr>
<td>DUCCS, 1994</td>
<td>Age ≤85 y; STEMI, ≤12 h§</td>
<td>250</td>
<td>Open label</td>
<td>APSAC 30 U over 2–5 min</td>
<td>UFH No bolus, 15 IU/kg per h for 4 d; target aPTT 50–90 s</td>
<td>No heparin 325 mg/d</td>
<td>Death, recurrent MI, recurrent ischemia, angiographic patency 14 d</td>
</tr>
</tbody>
</table>

APSAC indicates anisoylated plasminogen-streptokinase activator complex (anistreplase); aPTT, activated partial thromboplastin time; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MU, mega units; SK, streptokinase; and tPA, tissue plasminogen activator (alteplase). Trial name abbreviations are as expanded in Figure 2 legend.

*No dose adjustment unless otherwise specified.
†Started after 12 h in ISIS-2 Pilot and after 4 hours in DUCCS.
‡The initial aspirin dose was 300 mg PO in UK centers and 200 mg IV in continental European centers.
§Stratified by time to presentation: 0 to 6 h or 6 to 12 h.
events (4.2%) versus 21 events (3.4%); OR, 1.21; 95% CI, 0.67 to 2.18) up to day 7 or during hospitalization among patients treated with UFH compared with control (Table 5).

**LMWH Versus Placebo (4 Trials; n=16 943)**

**Designs of Included Studies**

Table 2 summarizes the study designs. Three trials used streptokinase, and the fourth used either streptokinase or urokinase for thrombolytic therapy. The initial dose of aspirin was between 100 and 325 mg followed by a maintenance dose of between 75 and 325 mg/d in the 3 trials in which this information was reported, and the duration of LMWH was between 1 and 11 days. Two trials evaluated dalteparin, 1 enoxaparin, and 1 reviparin.

**Study Quality**

Proper methods were used to generate the randomized treatment allocation, and the sequence was adequately concealed in the 2 studies that reported this information. All 4 studies were double-blind and placebo controlled, and follow-up was 99% in the 3 studies for which these data were reported.

**Outcomes**

**Reinfarction, Stroke, Death**

There was a significant reduction of approximately one quarter in reinfarction (134 events [1.6%] versus 184 events [2.2%]; OR, 0.72; 95% CI, 0.58 to 0.90; number needed to treat [NNT]=167) and a 10% reduction in death (659 events [7.8%] versus 730 events [8.7%]; OR, 0.90; 95% CI, 0.80 to 0.99; NNT=111) during hospitalization/at day 7 among patients treated with LMWH compared with placebo (Table 4, Figure 3). This benefit remained evident at day 30 for both reinfarction (168 events [2.1%] versus 219 events [2.7%]; OR, 0.76; 95% CI, 0.62 to 0.93; NNT=167) and death (787 events [9.7%] versus 900 events [11.1%]; OR, 0.86; 95% CI, 0.78 to 0.95; NNT=71) (Table 6). There was significant heterogeneity for the pooled estimate for reinfarction at day 30, which can be attributed to the large and unexpected almost 4-fold excess of reinfarction in the BIOMACS II study among patients treated with LMWH compared with placebo. However, this was a small study (n=101) with only a small number of reinfarctions (n=10), which were not significantly increased (OR, 3.91; 95% CI, 0.79 to 19.44).

There was a nonsignificant excess of strokes during hospitalization/at day 7 in patients treated with LMWH compared with placebo (68 events [0.8%] versus 57 events [0.7%]; OR, 1.19, 95% CI, 0.84 to 1.70). This was almost entirely accounted for by an increase in intracranial hemorrhage among patients treated with LMWH (23 events [0.3%] versus 10 events [0.1%]; OR, 2.18, 95% CI, 1.07 to 4.52; number needed to harm [NNH]=500). The increase in strokes with LMWH was also evident at 30 days (80 events [1.0%] versus 67 events [0.8%]; OR, 1.19; 95% CI, 0.86 to 1.65), but the absolute difference remained the same (a difference of 13 events at both time points).

**Bleeding**

Among the 1272 patients for whom the data were available, there was a significant excess of minor bleeding during hospitalization/at day 7 among patients treated with UFH compared with control (Table 5).
day 7 among those treated with LMWH compared with placebo (97 events [15.1%] versus 33 events [5.2%]; OR, 3.24; 95% CI, 2.12 to 4.91) (Table 3). This analysis included only 2 studies, and there was statistically significant heterogeneity between them (P = 0.003).

There also was a significant excess of major bleeds during hospitalization/at day 7 among 16 842 patients treated with LMWH compared with placebo (94 events [1.1%] versus 35 events [0.4%]; OR, 2.70; 95% CI, 1.83 to 3.99; NNH = 143).

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>N</th>
<th>Blinding</th>
<th>Randomized Treatment</th>
<th>LMWH*</th>
<th>UFH†</th>
<th>Aspirin</th>
<th>Primary Outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSENT 3, 2001</td>
<td>Age &gt;18 y; STEMI or LBBB, ≥6 h</td>
<td>4078</td>
<td>Open label</td>
<td>TNK  30–50 mg (weight adjusted)</td>
<td>Enoxaparin 1 mg/kg BID, ≥7 d</td>
<td>60 U/kg bolus, then 12 U/kg per h for 48 h</td>
<td>150–325 mg/d</td>
<td>In-hospital MI or RI or 30-day death</td>
<td>30 d</td>
</tr>
<tr>
<td>HART II, 2001</td>
<td>Age ≥18 y; STEMI or new LBBB, ≥12 h</td>
<td>400</td>
<td>Open label</td>
<td>tPA weight adjusted over 90 min</td>
<td>Enoxaparin 1 mg/kg BID, ≥3 d</td>
<td>4000–5000 IU bolus, then 15 IU/kg per hour for ≥3 d</td>
<td>Not specified</td>
<td>Angiographic 90-min TIMI flow</td>
<td>5–7 d</td>
</tr>
<tr>
<td>Baird et al, 2002</td>
<td>STEMI</td>
<td>300</td>
<td>Open label</td>
<td>SK 1.5 MU or APSAC 100 mg TID</td>
<td>Enoxaparin 40 mg TID, 4 d</td>
<td>5000 IU bolus, then 30 000 IU over 24 h for 4 d</td>
<td>75–300 mg/d after day 4</td>
<td>MI, death, readmit for UA</td>
<td>90 d</td>
</tr>
<tr>
<td>ENTIRE-TIMI 23, 2002</td>
<td>Age 21–75 y; STEMI, ≥6 h</td>
<td>242</td>
<td>Open label</td>
<td>TNK 0.53 mg/kg</td>
<td>Enoxaparin 1 mg/kg BID, ≥8 d</td>
<td>60 IU/kg, then 12 IU/kg per h for ≥3 d</td>
<td>100–325 mg/d§</td>
<td>Angiographic TIMI flow</td>
<td>30 d</td>
</tr>
<tr>
<td>ASSENT Plus, 2003</td>
<td>Age ≥18 y; STEMI or new LBBB, ≥6 h</td>
<td>439</td>
<td>Open label</td>
<td>tPA ≥100 mg over 90 min</td>
<td>Dalteparin first dose 90 IU/kg, then 120 IU/kg BID, 4–7 d</td>
<td>4000–5000 IU bolus, then 800–1000 IU/h for 48 h</td>
<td>150–325 mg/d§</td>
<td>Angiographic TIMI flow</td>
<td>30 d</td>
</tr>
<tr>
<td>ASSENT 3 Plus, 2003</td>
<td>Age ≥18 y; STEMI or new LBBB, ≥6 h</td>
<td>1639</td>
<td>Open label</td>
<td>TNK 30–50 mg (weight adjusted)</td>
<td>Enoxaparin 1 mg/kg BID, ≥7 d</td>
<td>60 IU/kg, then 12 IU/kg per h for ≥3 d</td>
<td>100–325 mg/d¶</td>
<td>In-hospital MI or RI or 30-day death</td>
<td>30 d</td>
</tr>
</tbody>
</table>

APSAC indicates anisoylated plasminogen-streptokinase activator complex (anistreplase); LV, left ventricular; MI, myocardial infarction; MU, mega units; RI, refractory ischemia; TIMI, Thrombolysis in Myocardial Infarction; SK, streptokinase; TNK, tenecteplase; tPA, tissue plasminogen activator (alteplase); and UA, unstable angina. Trial name abbreviations are as expanded in Figure 4 legend.

*All enoxaparin trials administered initial intravenous bolus of 30–40 mg. Initial intravenous bolus of dalteparin was 30 IU/kg.
†In each trial UFH was weight adjusted according to the results of the activated partial thromboplastin time.
‡No aspirin given during the first 4 days.
§Initial dose =160 mg PO or 250–500 mg IV.
¶Initial dose 150–325 mg/d.

No significant heterogeneity for any outcome. |
Reinfarction During Hospitalization*

<table>
<thead>
<tr>
<th>Study</th>
<th>UFH Control</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUCCS, 1994</td>
<td>9/128 4/122</td>
<td>2.23 0.70 - 7.44</td>
</tr>
<tr>
<td>ECGS, 1992</td>
<td>10/324 10/320</td>
<td>0.99 0.40 - 2.40</td>
</tr>
<tr>
<td>ISIS-2 Pilot, 1987</td>
<td>1/106 5/103</td>
<td>0.19 0.02 - 1.63</td>
</tr>
<tr>
<td>OSIRIS, 1992</td>
<td>2/64 1/64</td>
<td>2.03 0.18 - 22.99</td>
</tr>
<tr>
<td>Total</td>
<td>22/622 20/609</td>
<td>1.08 0.58 - 1.99</td>
</tr>
</tbody>
</table>

Death During Hospitalization

<table>
<thead>
<tr>
<th>Study</th>
<th>UFH Control</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUCCS, 1994</td>
<td>12/128 8/122</td>
<td>1.47 0.58 - 3.74</td>
</tr>
<tr>
<td>ECGS, 1992</td>
<td>9/324 11/320</td>
<td>0.80 0.58 - 1.96</td>
</tr>
<tr>
<td>ISIS-2 Pilot, 1987</td>
<td>8/106 6/103</td>
<td>1.32 0.44 - 3.85</td>
</tr>
<tr>
<td>OSIRIS, 1992</td>
<td>1/64 3/64</td>
<td>0.32 0.03 - 3.19</td>
</tr>
<tr>
<td>Total</td>
<td>30/622 28/609</td>
<td>1.04 0.62 - 1.78</td>
</tr>
</tbody>
</table>

LMWH Versus UFH (6 Trials; n=7098)

**Design of Included Studies**

Table 3 summarizes the study designs. Three studies used tenecteplase, 2 alteplase, and streptokinase. One study did not administer aspirin until day 4; the remaining studies administered at least 150 mg initially. The maintenance dose of aspirin was between 75 and 325 mg daily. Five of the 6 studies evaluated enoxaparin; the remaining study evaluated dalteparin. The duration of LMWH or UFH treatment was between 48 hours and 8 days.

**Study Quality**

Four studies reported information concerning the proper generation of the randomized treatment allocation sequence, and all trials reported adequate concealment of the randomized sequence treatment sequence. None of the studies were double-blind. In 5 studies follow-up was at least 99% complete, in the remaining study complete-ness of follow-up was not reported.

**Outcomes**

**Reinfarction, Stroke, Death**

There was a significant reduction of ≈45% in reinfarction (108 events [3.0%] versus 181 events [5.2%]; OR, 0.57; 95% CI, 0.45 to 0.73; NNT=45) and a nonsignificant 8% reduction in death (172 events [4.8%] versus 185 events [5.3%]; OR, 0.92; 95% CI, 0.74 to 1.13) during hospitalization/at day 7 among patients treated with LMWH compared with UFH (Table 4, Figure 4). A similar pattern was evident at day 30 for both reinfarction (103 events [3.7%] versus 150 events [5.6%]; OR, 0.64; 95% CI, 0.50 to 0.84; NNT=53) and death (201 events [5.6%] versus 211 events [6.0%]; OR, 0.94; 95% CI, 0.77 to 1.14) (Table 6, Figure 4).

There was a nonsignificant excess of strokes during hospitalization/at day 7 in patients treated with LMWH compared with UFH (66 events [1.8%] versus 47 events [1.3%]; OR, 1.38; 95% CI, 0.95 to 2.01). There was accompanied by a nonsignificant increase in intracranial hemorrhage among patients treated with LMWH (39 events [1.1%] versus 33 events [1.0%]; OR, 1.18; 95% CI,

**TABLE 5. Bleeding During Hospitalization/at 7 Days in Randomized Heparin Trials**

<table>
<thead>
<tr>
<th>Bleeding Outcome</th>
<th>Total N</th>
<th>UFH, n/N (%)</th>
<th>Control, n/N (%)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td>1022</td>
<td>101/516 (19.6%)</td>
<td>63/506 (12.5%)</td>
<td>1.72 (1.22–2.43)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1231</td>
<td>26/622 (4.2%)</td>
<td>21/609 (3.4%)</td>
<td>1.21 (0.67–2.18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding Outcome</th>
<th>Total N</th>
<th>LMWH, n/N (%)</th>
<th>Placebo, n/N (%)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding†</td>
<td>1272</td>
<td>97/641 (15.1%)</td>
<td>33/631 (5.2%)</td>
<td>3.24 (2.12–4.91)†</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>16842</td>
<td>94/8421 (1.1%)</td>
<td>35/8421 (0.4%)</td>
<td>2.70 (1.83–3.99)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding Outcome</th>
<th>Total N</th>
<th>LMWH, n/N (%)</th>
<th>UFH, n/N (%)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td>6393</td>
<td>739/3242 (22.8%)</td>
<td>612/3151 (19.4%)</td>
<td>1.26 (1.12–1.43)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7093</td>
<td>117/3591 (3.3%)</td>
<td>89/3502 (2.5%)</td>
<td>1.30 (0.98–1.72)</td>
</tr>
</tbody>
</table>

*No statistical heterogeneity for any bleeding outcome unless indicated otherwise.
†The CREATE study did not report minor bleeding.
‡P for heterogeneity 0.003.
At 30 days the nonsignificant increase in strokes remained evident (50 events [1.9%] versus 41 events [1.6%]; OR, 1.19; 95% CI, 0.86–1.65), but there were fewer events reported than at the earlier time point because 30-day stroke data were not available from 2 studies.51,54

### TABLE 6. Reinfarction, Death, and Stroke at 30 Days in Randomized Heparin Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total N</th>
<th>LMWH, n/N (%)</th>
<th>Placebo, n/N (%)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinfarction</td>
<td>16167</td>
<td>168/8087 (2.1%)</td>
<td>219/8080 (2.7%)</td>
<td>0.86 (0.62–0.93)†</td>
</tr>
<tr>
<td>Death</td>
<td>16167</td>
<td>787/8087 (9.7%)</td>
<td>900/8080 (11.1%)</td>
<td>0.86 (0.78–0.95)</td>
</tr>
<tr>
<td>Stroke</td>
<td>16167</td>
<td>80/8087 (1.0%)</td>
<td>67/8080 (0.8%)</td>
<td>1.19 (0.86–1.65)</td>
</tr>
</tbody>
</table>

*Unless indicated otherwise, there was no significant heterogeneity for any outcome.
†P for heterogeneity 0.02.
There was a significant increase in minor bleeding during hospitalization at day 7 among patients treated with LMWH compared with UFH (739 events [22.8%] versus 612 events [19.4%]; OR, 1.26; 95% CI, 1.12 to 1.43) (Table 5). A similar pattern was evident for major bleeds, although the increase was not significant (117 events [3.3%] versus 89 events [2.5%]; OR, 1.30; 95% CI, 0.98 to 1.72). In 2 trials intracranial hemorrhage was not included as part of major bleeding.

### Subgroup and Sensitivity Analyses

#### Different LMWH Preparations

Three different LMWH preparations (dalteparin \(n=2\), enoxaparin \(n=1\), reviparin \(n=1\)) were evaluated in the 4 trials that compared LMWH with placebo. When stratified by

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### Subgroup and Sensitivity Analyses

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Three different LMWH preparations (dalteparin \(n=2\), enoxaparin \(n=1\), reviparin \(n=1\)) were evaluated in the 4 trials that compared LMWH with placebo. When stratified by
LMWH preparation, there was significant heterogeneity for the outcome of reinfarction at 30 days and minor bleeding during hospitalization/at day 7 (data not shown). Both of these analyses included only 1 trial in each group, and chance or other differences among the trials may have accounted for this heterogeneity.

Only 2 different LMWH preparations (dalteparin [n=1], enoxaparin [n=5]) were evaluated in the 6 trials that compared LMWH with UFH, and the results stratified by LMWH preparation were not statistically heterogeneous for any outcome.

Trials With Fibrin-Specific Versus Non–Fibrin-Specific Thrombolytic Agents

One of 4 trials comparing UFH with placebo or no heparin used a more fibrin-specific agent, none of the 4 trials comparing LMWH with placebo used a fibrin-specific agent, and 5 of the 6 trials comparing LMWH with UFH used a more fibrin-specific agent. When stratified according to type of thrombolytic agent (fibrin-specific versus non–fibrin-specific agent), there was no significant heterogeneity for any outcome.

Sensitivity Analyses

Deleting individual studies yielded pooled results that were not significantly different from the overall pooled estimates, although in the comparisons of LMWH versus placebo, the statistically significant reductions in death and in myocardial infarction were no longer evident after removal of the Clinical Trial of Reiparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE). The funnel plot of effect size versus study precision for the outcomes of death and myocardial infarction demonstrated no asymmetry to suggest major publication bias.

Fixed Versus a Random Effects Model

For outcomes in which there was statistically significant heterogeneity among the studies, the pooled estimates obtained with the fixed effects model were no longer statistically significant with the random effects model (LMWH versus placebo at 7 days: minor bleeding: OR, 3.24; 95% CI, 2.12 to 4.91 with fixed effects model; OR, 3.62; 95% CI, 0.94 to 13.95 with random effects model; LMWH versus placebo at 30 days: myocardial infarction: OR, 0.76; 95% CI, 0.62 to 0.93 with fixed effects model; OR, 0.79; 95% CI, 0.30 to 2.09 with random effects model).

Discussion

Our results provide no evidence for a benefit of intravenous UFH for preventing reinfarction or death in patients with STEMI who are routinely treated with aspirin and thrombolysis. However, the UFH trials were underpowered because they included a total of only 1239 randomized patients with 42 reinfarctions and 58 deaths. This small number of events is reflected by the wide CIs for the estimates of treatment effect, which do not exclude moderate and plausible benefits or increases of 30% to 40% in reinfarction or death. More than 20 000 patients would have had to be randomized in these trials to reliably establish whether there was a modest but still worthwhile (eg, 20%) reduction in reinfarction or death with intravenous UFH in this setting.

Despite the lack of evidence of efficacy of UFH for preventing reinfarction or death, intravenous UFH remains widely used in patients with STEMI, particularly in Western countries in which fibrin-specific thrombolytic agents are widely used.55,56 This practice is consistent with current ESC and ACC/AHA guidelines for the management of STEMI, which recommend intravenous UFH for patients treated with alteplase or more fibrin-specific thrombolytic agents.5,6 Most randomized trials comparing different thrombolytic agents for the treatment of STEMI were performed with intravenous UFH, and newer fibrin-specific agents were approved on this basis. There is also evidence of improved infarct-related coronary artery patency when intravenous UFH is added to fibrin-specific thrombolytic agents.19,36,43 However, in 2 of these trials, patients treated with intravenous UFH did not receive aspirin,19,36 whereas in the third study,43 in which all patients received aspirin, there was only a modest impact of intravenous UFH on patency. Trials of other antithrombotic agents (eg, glycoprotein IIb/IIIa inhibitors) suggest that improved patency does not necessarily translate into improved clinical outcomes.57–60 In the absence of evidence of efficacy, concerns regarding safety assume greater importance. In the case of intravenous UFH, there is a consistent pattern of increased risk of bleeding for both major and intracranial bleeding and a significant increase in minor bleeding, which raises concerns of harm.

LMWH compared with placebo reduced reinfarction by 25% and death by 10%. Six reinfarctions and 9 deaths were prevented during hospitalization/at day 7 for every 1000 patients treated with LMWH, at the cost of 7 major bleeds, including 2 intracranial bleeds. By 30 days, 6 reinfarctions and 14 deaths were prevented for every 1000 patients treated. Stroke was not significantly increased, but the observed excess of strokes with LMWH was equivalent to an increase of 2 events for every 1000 treated. This indicates that the benefits outweigh the harm. These analyses are based on data from >16 000 patients with STEMI. There was no convincing evidence of heterogeneity among different LMWH preparations tested, but the number of trials was small, and most of the data were obtained from the 15 000-patient CREATE study in which reviparin was used.11

Pooled data from direct randomized comparisons indicate that LMWH compared with intravenous UFH reduced the risk of reinfarction by 43% with no reduction in death. Twenty-two reinfarctions were prevented during hospitalization/at day 7 for every 1000 patients treated with LMWH, at the cost of an increase in minor bleeding. By 30 days, 19 reinfarctions were prevented for every 1000 patients treated with LMWH. Although there was no significant difference in the incidence of stroke between the 2 treatment groups, stroke was increased among those treated with LMWH, equivalent to an increase of 5 events for every 1000 treated during hospitalization/at day 7 and 3 events for every 1000 patients treated by 30 days. These analyses are based on data from >7000 patients with STEMI. There was no statistical evidence of heterogeneity among the 2 LMWH preparations.

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tested, but most of the data were obtained from 5 studies in which enoxaparin was used.

One factor that may contribute to the difference in effectiveness of LMWH compared with UFH is differences in the duration of anticoagulation. In direct head-to-head comparisons, most patients receiving UFH were treated for 2 to 4 days, whereas those receiving LMWH were mostly treated for between 4 and 8 days. Meanwhile, the longer half-life of LMWH compared with UFH may have blunted or eliminated the rebound procoagulant effect that occurs after intravenous UFH is stopped.61 These data underscore the importance of an adequate duration of LMWH therapy when used as adjunctive therapy to thrombolysis in patients with STEMI.

The reduction in reinfarction with LMWH compared with UFH is consistent with indirect comparison of UFH versus control (no reduction in reinfarction) and LMWH versus placebo trials (28% reduction in reinfarction). However, it seems implausible that LMWH provides an even greater reduction in reinfarction (43%) in the active comparator trials versus UFH than when compared with placebo. Although intravenous UFH has not been shown to reduce reinfarction, the comparisons between UFH and control were severely underpowered, and a benefit cannot be excluded. The findings for reinfarction in the LMWH versus placebo compared with LMWH versus UFH trials could potentially also be explained by diagnostic suspicion bias because all of the LMWH versus UFH trials were open label, whereas all of the trials comparing LMWH with placebo were double-blind. Considerable judgment is needed to diagnose early reinfarction, whereas death and, to a lesser extent, major bleeding are not subject to this bias. However, the CIs for estimates from the pooled analyses of these 2 groups of trials overlap, and it is possible that the apparent contrast in their results for reinfarction is due to chance. Furthermore, indirect comparisons are unreliable and potentially misleading because of differences in the kinds of patients randomized, outcome definitions, and treatment regimens. For example, the UFH versus control trials were conducted during 1987–1994, and the LMWH versus placebo trials were conducted during 1997–2005. During this time there have been substantial changes in the way that reinfarction is diagnosed, which may have limited the ability of the early trials to reliably detect a treatment effect. LMWH versus placebo trials involved the use of first-generation thrombolytic agents, whereas direct comparisons between LMWH and UFH were performed primarily in patients treated with more fibrin-specific thrombolytic agents. The relative efficacy and safety of LMWH and UFH should be further clarified by the results of the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction Study 25 (ExTRACT-TIMI 25), which is currently comparing enoxaparin with UFH in 21 000 patients with STEMI who are eligible to receive fibrinolytic therapy.62

Collins et al17\(^\text{,}18\) performed a meta-analysis of 26 randomized trials involving 73 000 patients who received either UFH by any route (subcutaneous or intravenous) or no heparin as an adjunct to thrombolytic therapy in patients with acute STEMI. Unlike our data, the majority of patients included in this meta-analysis received UFH by the subcutaneous route.18\(^\text{,}20\) and 21 of the 26 included trials did not use routine aspirin therapy. An analysis restricted to trials that used aspirin revealed that UFH compared with no UFH significantly reduced the risk of death (8.6% versus 9.1%; \(P<0.03\)) and reinfarction (3.0% versus 3.3%; \(P=0.04\)).\(^\text{7} The however, major bleeding was also significantly increased (1.0% versus 0.7%; \(P<0.001\)), and these investigators concluded that routine administration of either intravenous or subcutaneous UFH as an adjunct to thrombolytic therapy in patients with acute STEMI was not warranted, irrespective of which thrombolytic agent was used. Other analyses restricted to patients who received intravenous UFH demonstrated no clear benefit of intravenous UFH.\(^\text{8,64}\) No large-scale trials of intravenous UFH have been conducted in patients with STEMI, and it seems very unlikely that they will be performed in the future given the emergence of LMWH, which is not only more effective but is much less likely to cause heparin-induced thrombocytopenia and in most patients can be administered in a fixed-weight adjusted dose without laboratory monitoring. Exceptions include patients undergoing invasive procedures and those with renal impairment because the anticoagulant effect of LMWH cannot be reversed and accumulates in patients with reduced creatinine clearance.

Several important questions remain unresolved. First, what is the role of LMWH in patients aged >75 years or with other risk factors for bleeding? As with all effective antithrombotic treatments, LMWH carries a risk of bleeding, and the balance between effectiveness and safety may be less favorable in patients at highest risk of bleeding.\(^\text{66}\) However, patients with risk factors for bleeding are also at increased risk of recurrent cardiovascular events and may therefore have the most to benefit from effective adjunctive antithrombotic therapies. Second, what is the role of LMWH in STEMI patients undergoing primary percutaneous coronary intervention? The ESC recommends that even after successful thrombolysis, patients should routinely undergo coronary angiography and percutaneous coronary intervention, if applicable.\(^\text{68}\) No study has evaluated LMWH for patients with STEMI undergoing percutaneous coronary intervention, although a subgroup analysis of the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial comparing LMWH with UFH in non–ST-elevation acute coronary syndrome in patients treated with an early invasive strategy that excluded patients who switched to a different anticoagulant at the time of randomization suggested that LMWH was more effective than UFH for preventing myocardial infarction or death at 30 days.\(^\text{66}\) However, most STEMI patients do not undergoing primary or even delayed percutaneous coronary intervention,\(^\text{67}\) and thus the results of our meta-analysis remain relevant to the majority of STEMI patients worldwide. Third, our meta-analysis was underpowered to reliably detect modest statistical heterogeneity or to explore potentially important subgroups. Finally, what is the role of LMWH in the context of new and emerging antithrombotic therapies for patients with STEMI? None of the LMWH trials were performed in patients treated with combined clopidogrel and
aspirin therapy, which has recently been shown to be superior to aspirin alone for preventing myocardial infarction or death in patients with STEMI.68 There have been no phase 3 trials directly comparing LMWH with direct thrombin inhibitors in patients with STEMI, but, unlike LMWH,11 direct thrombin inhibitors have not been shown to reduce death.69,70 Selective factor Xa inhibitors are currently being evaluated in the Michelangelo Organization to Assess Strategies for Ischemic Syndromes (OASIS) trials, which are comparing fondaparinux with usual care in 12 000 patients with STEMI who undergo pharmacological or catheter-based reperfusion therapy and with enoxaparin in 20 000 patients with acute coronary syndrome without ST elevation. Collectively, the EXTRACT and Michelangelo programs should further clarify the role of anticoagulant therapies in a range of patients with acute coronary syndrome, irrespective of whether or not there is ST elevation.

In conclusion, among aspirin-treated patients with STEMI who receive thrombolytic therapy, randomized trials comparing intravenous UFH with control have been underpowered and have not shown a benefit of UFH for preventing reinfarction or death. LMWH administered for 4 to 8 days compared with placebo reduces reinfarction by approximately one quarter and death by 10% and when directly compared with UFH reduces reinfarction by almost one half. The benefits of LMWH are seen early and remain evident at 30 days. These data suggest that LMWH should be the preferred antithrombin in this setting.

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Disclosure

Drs Eikelboom, Quinlan, Mehta, Turpie, Menown, and Yusuf have received honoraria for speaking at symposia sponsored by pharmaceutical companies that market low-molecular-weight heparin preparations.

References


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