Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction

The AMI–SK study

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Aims To establish whether the addition of enoxaparin (a low-molecular-weight heparin) to streptokinase therapy improves early and sustained coronary patency and clinical outcome in patients with evolving myocardial infarction.

Methods and Results A total of 496 patients with acute myocardial infarction treated with streptokinase were randomized to an intravenous bolus (30 mg) and subcutaneous injections (1 mg . kg⁻¹, twice daily) of enoxaparin (n=253), or placebo (n=243) for 3–8 days. The median duration of treatment in both groups was 5 days. ST-segment resolution at 90 min and 180 min measured by electrocardiogram was improved in patients receiving enoxaparin. Complete, partial and no ST-segment resolution at 180 min was observed in 36%, 44% and 19% in the enoxaparin group vs 25%, 44% and 31% in the placebo group, respectively (P=0·004). Assessment of the primary end-point revealed improved TIMI-3 flow with enoxaparin vs placebo (70% vs 58%, P=0·01). Combined TIMI-2 and -3 flow was also improved (88% vs 72%, P=0·001), as was TIMI frame count (P=0·003). The triple clinical end-point of death, reinfarction and recurrent angina at 30 days was reduced with enoxaparin (13% vs 21%, P=0·03).

Conclusion Streptokinase in combination with enoxaparin is associated with better ST-segment resolution and better angiographic patency at days 5–10, suggesting more effective reperfusion. This was associated with a significant reduction in clinical events, indicating less reocclusion.

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Key Words: Myocardial infarction, streptokinase, low-molecular-weight heparin, enoxaparin.

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30 days were recorded. Comes (death, reinfarction, and recurrent angina) at was assessed by electrocardiography, and clinical out-
flow) assessed by angiography after approximately 8 minutes. In addition, early reperfusion at 90 and 180 min
of glycoprotein IIb/IIIa antagonists was not permitted while the patient was on study medication, except when percutaneous angioplasty was performed. All patients were followed for 30 days.

**Efficacy parameters**

(1) Angiography was carried out on day 8 (range allowed=days 5 to 10). The primary efficacy parameter was the TIMI flow grade 3 of the infarct-related artery. Secondary efficacy angiographic parameters were: TIMI flow grades 2 and 3 (patency) and corrected TIMI frame count on day 8 angiography;
(2) Secondary efficacy parameters were: the incidence of successful reperfusion based on ST-segment resolution at 90 min and 180 min (ST-segment resolution was classified as complete (≥70% resolution), incomplete (30–70% resolution) or no resolution (<30% resolution); infarct size based on calculated myocardial enzyme release; and the incidence of clinical end-points of death, recurrent myocardial infarction or recurrent angina up to 30 days as single, double or triple end-points.

Reinfarction in the first 18 h was defined as recurrent symptoms of ischaemia at rest accompanied by new or recurrent ST-segment elevation ≥0·1 mV in at least two contiguous leads lasting ≥30 min. After 18 h the definition of reinfarction was recurrent symptoms of ischaemia at rest lasting ≥30 min and meeting the ECG criteria (new or recurrent persistent ST-segment elevation ≥0·1 mV or appearance of new, abnormal Q-waves in any two contiguous leads not showing ST-segment elevation on the qualifying ECG, or new left
bundle-branch block), or meeting enzyme criteria (further increases in concentrations of creatinine kinase MB, or total creatinine kinase above two times the upper limit of normal [three times post-percutaneous coronary intervention, five times post-coronary artery bypass grafting (CABG)] and increased over the previous value).

Recurrent angina was defined as one episode of angina at rest lasting >20 min or at least two episodes of angina at rest lasting >10 min within 24 h and associated with new ECG changes or resulting in an invasive cardiac intervention within the same hospitalization or rehospitalization for unstable angina.

Angiograms, electrocardiograms and cardiac enzymes were analysed by core laboratories blinded to treatment assignment. Clinical end-points were reviewed and adjudicated by an independent clinical review committee, blinded to treatment assignment.

Safety parameters

The primary safety parameter was the rate of major haemorrhage defined as haemorrhage resulting in death; transfusion of at least two packs of red blood cells or whole blood; 3 g. dl⁻¹ or greater fall in haemoglobin not associated with CABG; or any haemorrhage that was retroperitoneal, intracranial, intraocular, or required surgical intervention or decompression of a closed space to stop or control the event (e.g. cardiac tamponade). The rate of major haemorrhage according to the TIMI definition was also recorded: a fall in haemoglobin levels ≥5 g. dl⁻¹ not associated with CABG, intracranial haemorrhage, or cardiac tamponade[18]. Major haemorrhages and strokes were reviewed and adjudicated by the independent clinical review committee.

Statistical analysis

It was estimated that 200 evaluable patients per treatment group (i.e. a total of 400 evaluable patients) would be needed to achieve 80% power to demonstrate a relative increase of 22% in the number of patients reaching TIMI flow grade 3 with enoxaparin, assuming a TIMI flow grade 3 rate of 60% at day 8 for the placebo group and an alpha level of 5%. Chi-square tests were used to compare the efficacy and safety of the two treatment groups. For efficacy clinical end-points, ‘Time to first event’ analyses were performed using the Kaplan–Meier method and the log-rank test was used for comparison of treatment groups.

Wilcoxon score tests were used to compare continuous variables. Patients were considered to be evaluable if they were randomized, received streptokinase and study medication, and had an assessable TIMI flow grade at day 8 (range allowed=day 5 to 10). In order to achieve 400 evaluable patients it was estimated that 500 patients should be enrolled.

### Results

#### Patient characteristics

In all, 496 patients were randomized, of whom 491 were treated with streptokinase and study medication. The baseline characteristics were similar among the two treatment groups (Table 1). The median time from symptom onset to streptokinase treatment was 3·3 h in the enoxaparin group (range 0·5–11·8) and 2·8 h in the placebo group (range 0·6–11·3), while the median time to the first dose of study drug was 3·7 h in the enoxaparin group and 3·3 h in the placebo group. Median duration of treatment was 5 days (range 0–15) and patients were discharged after a median 11 days in both groups.

#### Efficacy

Coronary angiography was performed in 436 patients. The infarct was related to the left anterior descending artery in 36% to the left circumflex in 15% and to the right coronary artery in 48%. The distribution of infarct-related vessels was similar in the two randomized patients groups.

Four hundred and twenty seven patients had an assessable TIMI flow and 389 were considered evaluable (angiography on days 5–10) and had adequate quality for assessment of coronary perfusion. In the evaluable population, significantly more patients receiving enoxaparin had TIMI grade 3 flow compared with those receiving placebo (primary efficacy parameter 70·3% vs 57·8%, \(P=0·01\), Fig. 1). Also corrected TIMI frame count (Fig. 2, \(P=0·003\)) and coronary patency (TIMI flow grades 2 or 3) on days 5–10 were better with enoxaparin 87·6% vs 71·7% for patients receiving placebo (\(P<0·001\)). The results were similar when all 427 patients with angiography were analysed (TIMI grade 3 flow 68·2% vs 55·7%, \(P=0·008\)).

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients randomized</td>
<td>253</td>
<td>243</td>
</tr>
<tr>
<td>Number of patients treated</td>
<td>252 (99·6)</td>
<td>239 (98·4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62·8 ± 11·7</td>
<td>62·9 ± 11·9</td>
</tr>
<tr>
<td>Males</td>
<td>183 (72·3)</td>
<td>193 (79·4)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>24 (9·5)</td>
<td>33 (13·6)</td>
</tr>
<tr>
<td>Prior angina</td>
<td>67 (26·5)</td>
<td>74 (30·5)</td>
</tr>
<tr>
<td>Previous aspirin user</td>
<td>40 (15·9)</td>
<td>49 (20·2)</td>
</tr>
<tr>
<td>Family history CAD</td>
<td>64 (25·3)</td>
<td>51 (21·0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>102 (40·3)</td>
<td>99 (40·7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>101 (39·9)</td>
<td>106 (43·6)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>83 (32·8)</td>
<td>76 (31·3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43 (17·0)</td>
<td>36 (14·8)</td>
</tr>
</tbody>
</table>

All values are patient numbers (percentages); age, mean ± SD. MI=myocardial infarction; CAD=coronary artery disease.
By electrocardiography, 15.7% of the enoxaparin-treated group achieved complete resolution of the ST segment at 90 min compared with 11.2% in the placebo-treated group, while the corresponding figures at 180 min were 36.3% vs 25.4%. Differences in the ST-segment resolution categories were highly significant \((P = 0.012\) at 90 min and \(P = 0.004\) at 180 min, respectively, Table 2), indicating improved reperfusion when streptokinase is combined with enoxaparin. Yet, no significant differences were achieved in infarct size, as assessed in 479 patients: mean values 5.1 vs 5.3 geq HBDH. \(1^{-1}\) in the enoxaparin and placebo group. Also ejection fraction in 177 patients was not significantly different: 55% vs 51% respectively.

Clinical events were less frequent in patients allocated to enoxaparin (Table 3). Particularly the rate of the triple end-point of death, myocardial infarction or recurrent angina in the enoxaparin-treated group was 36% lower than in the placebo group at day 30 (13.4% vs 21.0%, \(P = 0.03\)). Regarding the single end-points the largest difference was apparent in the rate of recurrent myocardial infarction which was statistically significant (Table 3). The difference between the two treatments was established early, increased during the first 2 weeks, and was sustained up to day 30 (Fig. 3). There were no statistically significant differences in the incidence of revascularization at day 30, but there was a trend toward less urgent revascularization in the enoxaparin group (Table 3).

### Table 2 ST-segment resolution

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Placebo</th>
<th>Significance ((P))</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 90 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>15(\cdot)7</td>
<td>11(\cdot)2</td>
<td>(0.012)</td>
</tr>
<tr>
<td>Partial</td>
<td>46(\cdot)7</td>
<td>37(\cdot)8</td>
<td></td>
</tr>
<tr>
<td>No resolution</td>
<td>37(\cdot)6</td>
<td>51(\cdot)1</td>
<td></td>
</tr>
<tr>
<td>At 180 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>36(\cdot)3</td>
<td>25(\cdot)4</td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>44(\cdot)4</td>
<td>43(\cdot)5</td>
<td>(0.014)</td>
</tr>
<tr>
<td>No resolution</td>
<td>19(\cdot)2</td>
<td>31(\cdot)0</td>
<td></td>
</tr>
</tbody>
</table>

All values given as percentages. Between brackets, number of electrocardiograms analysed.

![Figure 1](image1.png)

**Figure 1** Patency (TIMI grade 2 or 3) at 8 days (evaluable population, \(n=389\)). TIMI = thrombolysis in myocardial infarction.

![Figure 2](image2.png)

**Figure 2**

### Table 3 Efficacy as reflected in clinical events at day 30

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Placebo</th>
<th>Significance ((P))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients randomized</td>
<td>253</td>
<td>243</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6(\cdot)7</td>
<td>7(\cdot)0</td>
<td>ns</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>2(\cdot)4</td>
<td>7(\cdot)4</td>
<td>(0.01^*)</td>
</tr>
<tr>
<td>Reangina</td>
<td>5(\cdot)9</td>
<td>9(\cdot)1</td>
<td>ns</td>
</tr>
<tr>
<td>Death or recurrent MI</td>
<td>9(\cdot)1</td>
<td>13(\cdot)2</td>
<td>0.15</td>
</tr>
<tr>
<td>Death, recurrent MI or angina</td>
<td>13(\cdot)4</td>
<td>21(\cdot)0</td>
<td>0.03</td>
</tr>
<tr>
<td>Death, recurrent MI or angina leading to revascularization</td>
<td>13(\cdot)0</td>
<td>18(\cdot)5</td>
<td>0.09</td>
</tr>
<tr>
<td>Any revascularization</td>
<td>29(\cdot)6</td>
<td>28(\cdot)0</td>
<td>ns</td>
</tr>
<tr>
<td>PCI</td>
<td>28(\cdot)1</td>
<td>26(\cdot)3</td>
<td>ns</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>5(\cdot)5</td>
<td>9(\cdot)5</td>
<td>ns</td>
</tr>
</tbody>
</table>

All values given as percentages. *Unplanned analyses. MI = myocardial infarction; PCI = percutaneous coronary intervention; ns = not significant.
Safety

By day 30, there were more major haemorrhages reported in the enoxaparin group than in the placebo group, although this difference was not statistically significant (Table 4). All major haemorrhages occurred within the first 8 days. No occurrences of stroke, whether haemorrhagic or embolic, were reported in the enoxaparin group, compared to 1·3% in the placebo group. This difference was not statistically significant.

The serious adverse-event profile was similar in both groups. There were 17 deaths in each group at 30 days of follow-up, representing 6·7% in the enoxaparin patients and 7·0% in the placebo group. The principal cause of death was congestive heart failure, accounting for 10 patients in the enoxaparin groups and 8 in the placebo group.

Table 4 Safety as reflected in clinical events at day 30

<table>
<thead>
<tr>
<th>Number of patients treated</th>
<th>Enoxaparin 252</th>
<th>Placebo 239</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major haemorrhage</td>
<td>4·8</td>
<td>2·5</td>
<td>0·2</td>
</tr>
<tr>
<td>Hb decline ≥ 3 g. dl⁻¹</td>
<td>4·4</td>
<td>2·1</td>
<td></td>
</tr>
<tr>
<td>Hb decline requiring transfusion ≥ 2 units packed red cells</td>
<td>0·8</td>
<td>1·3</td>
<td></td>
</tr>
<tr>
<td>TIMI major haemorrhage</td>
<td>1·6</td>
<td>0·8</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>0·0</td>
<td>0·4</td>
<td></td>
</tr>
<tr>
<td>Any stroke</td>
<td>0·0</td>
<td>1·3</td>
<td>0·1</td>
</tr>
</tbody>
</table>

All values given as percentages. Hb=haemoglobin; TIMI=thrombolysis in myocardial infarction; ICH=intracranial haemorrhage.

Discussion

The findings in this study indicate that, in patients with evolving myocardial infarction treated with streptokinase and aspirin, adjunctive therapy with enoxaparin facilitates early coronary reperfusion and reduces the risk of reocclusion, resulting in improved clinical outcome. Improved early coronary reperfusion is implied in greater resolution of the ST segment as analysed 90 min and 180 min after randomization. The relationship between ST-segment resolution and early angiographic patency has been established in several studies, and among patients with normal TIMI-3 epicardial coronary flow, those patients with complete ST-segment resolution have a significantly better outcome than patients with incomplete or no resolution. The prevention of reocclusion by enoxaparin is apparent by the reduction in clinical events, particularly reinfarction, and better coronary perfusion at the 5–10 day coronary angiography, which was the primary study end-point.

Reperfusion and reocclusion

This is the first study documenting improved coronary reperfusion with anticoagulant therapy in patients receiving streptokinase. GUSTO-I compared early intravenous administration of unfractionated heparin, started at the same time as the fibrinolytic drugs, and subcutaneous unfractionated heparin, started after 4 h in patients receiving streptokinase. The latter regimen was also studied in GISSI-2 and ISIS-3. Angiographic findings at 90 and 180 min were similar among patients receiving immediate intravenous and deferred subcutaneous heparin with streptokinase at 90 and 180 min. In a recent placebo-controlled trial, dalteparin (another low molecular weight heparin) was
investigated as an adjunct to thrombolysis with streptokinase and provided a non-significant trend toward increased TIMI grade 3 patency at 20–28 h after randomization, and non-invasive signs of early (90 min) reperfusion, favouring low-molecular-weight heparin [19]. Adjunctive therapy with the glycoprotein IIb/IIIa receptor blocker eptifibatide in patients treated with streptokinase also improved early coronary perfusion, but bleeding rates were excessive, and this combination of therapy was not pursued [20].

With fibrin specific fibrinolytics, such as alteplase, adjunctive unfractionated heparin has shown to improve early and subsequent patency of the infarct-related artery [44–61], albeit not in all studies [21]. The Heparin–Aspirin Reperfusion Trial (HART II) demonstrated that enoxaparin in conjunction with recombinant tissue plasminogen activator was at least as effective as unfractionated heparin in achieving infarct-related coronary artery patency 90 min after the onset of treatment, with a trend toward higher rates of TIMI-3 flow (53% vs 48%) [22]. Similarly, a trend was demonstrated for lower rates of reocclusion with enoxaparin compared with unfractionated heparin (3-1% vs 9-1%). Similar trends toward less reocclusion were observed in patients receiving dalteparin or pentasaccharide vs unfractionated heparin [23,24].

More recently, the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 study examined the efficacy and safety of three different thrombolytic regimens (tenecteplase plus enoxaparin, low-dose tenecteplase plus abciximab and unfractionated heparin, and tenecteplase plus unfractionated heparin) in 6095 patients [25]. In this study, patients receiving enoxaparin and tenecteplase had a significantly lower rate of clinical events (composite of 30 day mortality, in-hospital reinfarction and in-hospital refractory ischaemia) than those receiving unfractionated heparin (11-4% vs 15-4%, \( P=0.0002 \)). Bleeding rates were higher with enoxaparin, but not significantly so. Reduced event rates were also observed with tenecteplase and unfractionated heparin and abciximab, compared to tenecteplase and unfractionated heparin, but bleeding rates were significantly higher with the abciximab combination. The present AMI–SK study extends these observations to patients initially treated with streptokinase. Thus, it is implied that continuation of such therapy does reduce the risk of thrombus extension or reocclusion and results in better patient outcome. Other recent studies indicated that long-term intensive anticoagulation with coumadin also reduces the risk of reocclusion after thrombolytic therapy [11,26] and improves outcome after myocardial infarction in general [11].

**Limitations**

In the present study no significant differences were observed in left ventricular ejection fraction or infarct size. Nevertheless close relations between coronary reperfusion, ejection fraction and infarct size were established in other studies [10,27,28]. The absence of significant differences in ejection fraction or infarct size in the present study is due, most likely, to relatively low sample size, and the missing data in part of the patients.

**Outcome**

Improved outcome was documented in the present study with enoxaparin, but was not observed with unfractionated heparin, given subcutaneously or intravenously after streptokinase in earlier megatrials [7–9]. The different findings in AMI–SK may be related to the early initiation of antithrombotic therapy by intravenous bolus injection, and to several pharmacological advantages of low-molecular-weight heparin over unfractionated heparin. First, stable high-intensity anticoagulation is achieved without the need for monitoring coagulation parameters such as activated partial thromboplastin time. Furthermore, low-molecular-weight heparins have a greater anti-Xa activity relative to the anti-IIa activity (about 4:1 vs 1:1 for unfractionated heparin). In patients with evolving myocardial infarction, receiving fibrinolytic therapy, platelets are activated, as well as factor Va, resulting in enhanced factor Xa activity, and thrombin generation [29,30]. Prevention of such thrombin generation by low-molecular-weight heparin may be more effective than thrombin inhibition with unfractionated heparin. This is supported by studies in a canine thrombosis model, in which enoxaparin in comparison with heparin more effectively increased perfusion and decreased thrombus mass [31].

Low-molecular-weight heparins have been studied extensively in acute coronary syndromes, particularly in patients admitted with unstable angina or suspected evolving myocardial infarction, without persistent ST-segment elevation [32–40]. The results show superiority over placebo [30] and clinical efficacy at least equal to unfractionated heparin [33–40]. In the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) and TIMI 11B studies, enoxaparin in comparison with unfractionated heparin resulted in a reduced rate of thrombotic complications: death, reinfarction and recurrent angina [33,34]. The current AMI–SK study extends these observations to patients with ST-segment elevation myocardial infarction, receiving streptokinase. Patients treated with unfractionated heparin may show a rebound with thrombotic events occurring early after discontinuation of such therapy [37]. Similar observations were made with dalteparin in the Fragmin During Instability in Coronary Artery Disease (FRISC) study [52]. In contrast, no rebound was observed after discontinuation of enoxaparin in the present study.

**Bleeding**

A combination of streptokinase and enoxaparin did increase bleeding complications, albeit not statistically

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significant. In the current AMI-SK study, no intracranial haemorrhages occurred in patients receiving streptokinase with enoxaparin, but more experience of using enoxaparin with streptokinase is needed to establish the safety and the net clinical benefit of the regimen.

Conclusion

Streptokinase is the most widely used fibrinolytic agent worldwide, in spite of studies showing superiority of more fibrin-specific fibrinolytic agents\(^9\). This preference for streptokinase is based predominantly on financial considerations, since fibrin-specific fibrinolytic agents are considerably more expensive. If the findings in the current study are confirmed in a larger clinical trial, a combination of streptokinase and enoxaparin may offer an effective thrombolytic regimen, at an acceptable cost level. Preparations for such a large clinical trial are ongoing.

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References

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Appendix 1

Contributors

M. L. Simoons, F. Bigonzi, F. Gosset, V. Le Louer, designed the study protocol, which was reviewed and approved by the steering committee. V. Le Louer and V. Keraudren performed the statistical analysis. F. Gosset collected and monitored the data. F. Didier performed the data management. M. L. Simoons wrote the manuscript. Aventis Pharma provided editorial help. All other authors reviewed and revised the manuscript.

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The FRAX.I.S. Study group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX.I.S. (FRAXiparine in Ischemic Syndrome). Eur Heart J 1999; 20: 1553–62.

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Appendix 1

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M. L. Simoons, F. Bigonzi, F. Gosset, V. Le Louer, designed the study protocol, which was reviewed and approved by the steering committee. V. Le Louer and V. Keraudren performed the statistical analysis. F. Gosset collected and monitored the data. F. Didier performed the data management. M. L. Simoons wrote the manuscript. Aventis Pharma provided editorial help. All other authors reviewed and revised the manuscript.

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