Low Molecular Weight Heparin Versus Regular Heparin or Aspirin in the Treatment of Unstable Angina and Silent Ischemia

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Objectives. This study was designed to test the hypothesis that low molecular weight heparin may lessen the severity of ischemic events in patients with unstable angina.

Background. Unstable angina is a thrombotic process that requires intensive medical treatment. Although current treatments can reduce the number of complications, serious bleeding continues to occur. Nadroparin calcium, a low molecular weight heparin, seems to be a safe therapeutic agent that does not require laboratory monitoring.

Methods. A total of 219 patients with unstable angina entered the study at a mean time of 6.17 h after the last episode of rest pain. Patients were randomized to receive aspirin (200 mg/day [group A]), aspirin plus regular heparin (400 IU/kg body weight per day intravenously and titrated by activated partial thromboplastin time [group B]) and aspirin plus low molecular weight heparin (214 UIC/kg anti-Xa twice daily subcutaneously [group C]). The major end points determined for the in-hospital period were 1) recurrent angina, 2) myocardial infarction, 3) urgent revascularization, 4) major bleeding, and 5) death. Minor end points were 1) silent myocardial ischemia, and 2) minor bleeding. Event rates were tested by chi-square analysis.

Results. Recurrent angina occurred in 37%, 44% and 21% of patients in groups A, B and C, respectively, and was significantly less frequent in group C than in either group A (odds ratio 2.26, 95% confidence interval [CI] 1 to 5.18, p = 0.03) or group B (odds ratio 3.07, 95% CI 1.26 to 7.00, p = 0.002). Nonfatal myocardial infarction was present in seven patients in group A, four in group B and none in group C (group B vs. A, p = 0.5; group C vs. A, p = 0.01). Urgent revascularization was performed in nine patients in group A, seven in group B and one in group C (C vs. A, p = 0.01). Two episodes of major bleeding occurred in group B. Silent myocardial ischemia was present in 38%, 41% and 25% of patients in groups A, B and C, respectively, and was significantly less frequent in group C than group B (odds ratio 2.12, 95% CI 0.97 to 4.69, p = 0.04). Minor bleeding was detected in 10 patients in group B, 1 patient in group C (B vs. C, p = 0.01) and no patient in group A (A vs. B, p = 0.003).

Conclusions. In this study, treatment with aspirin plus a high dose of low molecular weight heparin during the acute phase of unstable angina was significantly better than treatment with aspirin alone or aspirin plus regular heparin.

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Coronary studies suggest that unstable angina results from thrombus formation and platelet aggregation. These thrombotic processes are generally mediated by thrombin, dependent on the action of platelets and not completely responsive to conventional therapy with aspirin and heparin (1). Nevertheless, pharmacologic studies (2–4) using antithrombotic agents in patients with unstable angina have demonstrated their beneficial effect in this coronary syndrome. Clinical studies (2–5) comparing aspirin and heparin in unstable angina have shown no significant differences among heparin, aspirin or a combination of both drugs.

In a previous study (6) we demonstrated biochemical differences between patients with an acute myocardial infarction and patients with unstable angina or silent myocardial ischemia. We observed that thrombotic reactant markers were significantly elevated in patients with unstable angina and also during episodes of silent myocardial ischemia. Other studies (7–9) have also shown that local phenomena such as vasospasm may precipitate myocardial ischemia. Therefore, thrombosis and thrombolysis appear to be important mechanisms in unstable angina and silent ischemia.

Low molecular weight heparin is absorbed onto the vascular endothelium and results in the increased release of tissue plasminogen activator (10,11). It has high antifactor Xa and antithrombin activities. The drug may have interference with platelets, reduces thrombin-induced platelet aggregability, causes less enhancement of aggregation induced by adenosine diphosphate (12) and significantly reduces fibrinogen levels in patients with a coronary artery syndrome (13,14).

The purpose of the present study was to determine whether a high dose of low molecular weight heparin combined with
aspirin is more beneficial than aspirin alone, or aspirin plus regular heparin, during the acute phase of unstable angina.

**Methods**

The study was a prospective, randomized, single-blind trial of antithrombotic therapy for patients admitted to the coronary care unit with acute chest pain due to unstable angina. A total of 219 patients gave written informed consent and were randomized.

**Inclusion criteria.** The following inclusion criteria were used: 1) Men or women >21 years old. 2) Unstable angina, defined as recent onset or prolonged (≥10 min), spontaneous rest pain occurring within 24 h of randomization. 3) Evidence of underlying ischemic heart disease as shown by at least one of the following: a) electrocardiographic (ECG) ischemic changes; b) previous documented myocardial infarction; c) previous coronary artery bypass surgery; d) history of typical exertional angina; e) previous coronary angiography showing ≥70% lumen narrowing in any coronary artery; f) angina at rest without acute ECG changes (diagnosed by two cardiologists); and g) positive stress test for angina or ST segment depression in the last month, or both. 4) Informed consent.

**Exclusion criteria.** The following exclusion criteria were used: 1) Acute Q or non-Q wave myocardial infarction. 2) Left bundle branch block. 3) Angina due to pulmonary edema; tachyarrhythmia; valvular heart disease; status post acute or postsubacute myocardial infarction (<12 weeks after infarction); thyrotoxicosis; hypertension; anemia (hemoglobin <11 g/dl). 4) Angioplasty within 3 months. 5) Contraindications to anticoagulation or nonsteroid anti-inflammatory drugs. 6) Use of anticoagulant drugs. 7) Presence of a terminal disease. 8) Pregnancy. 9) Implanted pacemaker.

**Design of the study.** Patients were randomized to one of three groups: group A = aspirin alone (200 mg/day orally) in accordance with the recommendations of the Third American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (15) plus saline solution infusion and bolus as placebo for heparin; group B = aspirin (200 mg/day orally) plus continuous infusion of intravenous heparin (400 IU/kg body weight per day), using a weight-adjusted heparin nomogram preceded by a bolus of 5,000 IU of heparin designed to raise the activated partial thromboplastin time to twice the control level and titrated daily; and group C = aspirin (200 mg/day orally) plus 214 units Institute Choay [UIC]/kg anti-Xa of low molecular weight heparin (CY 216 nadroparin calcium) twice daily subcutaneously and saline solution infusion and bolus as placebo for heparin. Patients with previous aspirin use were also randomized if this drug was being taken irregularly. In all patients the antithrombotic therapy was discontinued by day 5 to 7 of admission (in-hospital period) or if a primary end point (see later) was reached or a definitive decision was made to perform an interventional procedure or provide ongoing medical treatment.

**Medical treatment.** Treatment with standard antianginal therapy (beta-adrenergic blocking agents, calcium channel blockers or intravenous nitrates, alone or in combination), was begun immediately on randomization. Continuation of predmission medications was recommended; the dosage was increased or another antianginal drug was added. The doses were increased as tolerated to obtain a systolic blood pressure of ≤130 mm Hg and a heart rate of ≤60 beats/min.

**Laboratory tests.** Serum total creatine kinase and its MB fraction were analyzed every 6 h for the initial 24 h to exclude acute myocardial infarction, and measurements were repeated every 12 h thereafter. Activated partial thromboplastin times were also obtained once daily or more, according to the recommendations of the hemostasis team, and were titrated by activated partial thromboplastin time until maintained at two times the normal values. An activated partial thromboplastin time basal control measurement was also obtained in patients in both groups A and C. Except for this control measurement, coagulation variables were not measured routinely in patients receiving low molecular weight heparin (group C).

**ECG monitoring.** The ST segment was monitored continuously during the 1st 48 h of admission with the use of two channels of a Siemens Sirecust 960 electrocardiograph. Leads were positioned according to the jeopardized area in patients presenting with acute ECG ischemic changes and positioned according to standard locations in patients without ischemic changes. The device was programmed to detect ST segment alteration; an alarm signal sounded if an ST segment shift ≥2 mm appeared. At least one complete 12-lead ECG was obtained in each patient daily.

**Coronary angiography.** Coronary angiography, when indicated, was performed a mean of 4.73 days after randomization. This delay was in accord with current practice in our institution and was not influenced by the patients’ inclusion in the trial.

**Primary end points.** The following events were defined as primary end points: 1) Recurrent angina, defined as chest pain at rest that lasted ≥10 min with or without ST segment changes but under an appropriate anti-ischemic schedule, with a heart rate <60 beats/min and systolic blood pressure <130 mm Hg. 2) Acute myocardial infarction, defined as the sudden development of new Q waves or non-Q wave ECG changes associated with increased levels of creatine kinase MB fraction >50 IU/liter (normal reference range 0 to 25 IU/liter). 3) Urgent intervention (coronary angioplasty or bypass surgery) when symptoms and signs were uncontrolled despite a full medical schedule (five drugs, including antiplatelet agents, anticoagulant agents, beta-adrenergic blocking agents, calcium channel antagonists and intravenous nitroglycerin). 4) Major bleeding, defined as a decrease in hemoglobin ≥2 g/dl or the need for transfusion, or both. 5) Death.

**Secondary end points.** Two events were defined as secondary end points: 1) Silent ischemia, defined as an episode of ECG changes without pain registered when the alarm signal sounded. It was considered an unsatisfactory outcome when it was present during the 1st 48 h. Patients with this finding were not excluded from the study but their therapy was adjusted intensively. 2) Minor bleeding, defined as spontaneous hematomas or bleeding at the puncture sites.
Statistical analysis. A sample size of 315 patients was based on a projected 36% rate of events (mortality 1%, myocardial infarction 3%, recurrent angina 17%, silent myocardial ischemia 13%, bleeding 2%) to detect a 50% reduction in end point (confidence level or 1 α 95% and power of 1 β 80%).

Analysis was based on intention to treat. Comparisons of baseline characteristics and events were performed by using a chi-square statistics or t test, as appropriate. A two-tailed Fisher exact test was used if there was an expected value of <5. Odds ratios were computed by Cornfield 95% confidence limit. An exploratory analysis of data was performed with Epi Info Version 5.0 (World Health Organization, Geneva, Switzerland). A p value < 0.05 was considered significant.

Results

Of the 663 patients with angina who were evaluated for entry into the study between May 1993 and July 1994, 444 did not meet the criteria for eligibility. All patients were admitted because of unstable angina with chest pain in the previous 24 h. Patients ≥80 years of age, those who recently underwent angioplasty or bypass surgery, those with a Q or non-Q wave acute myocardial infarction or angina after acute myocardial infarction and those receiving long-term and appropriate aspirin treatment were the basis for nearly 100% of the exclusions.

Of the 219 patients randomized, 8 were later excluded—6 because their participation was refused by their physician and 2 because they subsequently had normal coronary angiographic findings.

Of the remaining 211 patients, 73 (group A) were randomly assigned to receive aspirin, 70 (group B) to receive aspirin plus intravenous heparin and 68 (group C) to receive aspirin plus low molecular weight heparin.

Groups were similar with respect to all pretreatment characteristics, including age, gender and clinical, ECG and angiographic features (Tables 1 and 2). At the time of admission 121 patients were taking beta-blockers, 89 were taking calcium channel antagonists, 143 were taking aspirin, 32 were taking angiotensin-converting enzyme inhibitors and 72 were taking nitrates.

Angiography was not required in 53 patients (25%) who were satisfactorily discharged in accordance with our institutional criteria, which did not indicate a need for this procedure.

Patients who did not reach a defined end point were discharged between 5 and 7 days after admission, free of symptoms and instructed to follow conventional therapy with aspirin and their baseline medications. This point was achieved by 41% of patients in group A, 37% in group B and 78% in group C. The remaining patients all reached an end point within this period (27% within the 1st 48 h; Table 3).

Recurrent chest pain despite full therapy led to urgent coronary angiography in 17 patients (11%). Three-vessel coronary disease was common in the three groups (25%, 42% and 44%, respectively). Left main coronary artery disease associated with one- or two-vessel disease was present in 13%, 8% and 15% of patients, respectively, in each group (Table 2). All indexes studied were somewhat unequally distributed among the groups (p = NS).

Primary end points. Major events occurred in 59%, 63% and 22% of patients in groups A, B and C, respectively, and were significantly less frequent in group C than in group A (odds ratio 5.06, 95% CI 2.28 to 11.39, p = 0.00001) or group B (odds ratio 5.63, 95% CI 2.50 to 12.81, p = 0.00001).

Recurrent angina occurred in 37%, 44% and 21% of patients in groups A, B and C, respectively, and was significantly less frequent in group C than in group A (odds ratio 2.26, 95% CI 1 to 5.18, p = 0.03) or group B (odds ratio 3.07, 95% CI 1.36 to 7.00, p = 0.002).

Nonfatal myocardial infarction was present in seven patients in group A, four in group B and none in group C (group C vs. A, p = 0.01; group B vs. A, p = 0.5). Urgent revascularization was performed in nine patients (12%) in group A,

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Group A (n = 73)</th>
<th>Group B (n = 70)</th>
<th>Group C (n = 68)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>64.1</td>
<td>63.5</td>
<td>62.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Smoker</td>
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<td>31</td>
<td>29</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48</td>
<td>51</td>
<td>47</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>33</td>
<td>25</td>
<td>26</td>
<td>0.4</td>
</tr>
<tr>
<td>Prior AMI</td>
<td>23</td>
<td>26</td>
<td>22</td>
<td>0.7</td>
</tr>
<tr>
<td>Prior PTCA or CABG</td>
<td>22</td>
<td>29</td>
<td>21</td>
<td>0.2</td>
</tr>
<tr>
<td>Prior angina*</td>
<td>41</td>
<td>38</td>
<td>27</td>
<td>0.8</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>30</td>
<td>30</td>
<td>29</td>
<td>0.9</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>41</td>
<td>41</td>
<td>39</td>
<td>0.9</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>0.7</td>
</tr>
</tbody>
</table>

* >180 days of evolution. Unless otherwise indicated, data are expressed as number (%) of patients. ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; Group A = patients receiving aspirin alone; Group B = patients receiving aspirin plus intravenous heparin; Group C = patients receiving aspirin plus low molecular weight heparin; PTCA = percutaneous transluminal coronary angioplasty.

Table 2. Randomization and Angiographic Data in the Three Study Groups

<table>
<thead>
<tr>
<th>Group A (n = 73)</th>
<th>Group B (n = 70)</th>
<th>Group C (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time to randomization (h)</td>
<td>6.05</td>
<td>6.4</td>
</tr>
<tr>
<td>Mean time to angiography (days)</td>
<td>5</td>
<td>4.2</td>
</tr>
</tbody>
</table>

CAGD

1-vessel | 10.55 (18%) | 10.55 (20%) | 10.55 (21%) |
2-vessel | 18.55 (33%) | 18.55 (34%) | 18.55 (34%) |
4-vessel | 23.55 (42%) | 23.55 (42%) | 23.55 (42%) |
Left main with 1- or 2-vessel | 7.55 (13%) | 4.55 (7%) | 7.55 (11%) |

Unless otherwise indicated, data are expressed as number (%) of patients. Definitions of groups as in Table 1. CAGD = coronary artery disease.
Table 3. Duration of the Study (in-hospital) for the Three Study Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>End Points (1st 48 h)*</th>
<th>End Points (day 2 to 6)</th>
<th>Discharged (day 5 to 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>A (n = 73)</td>
<td>22</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>B (n = 70)</td>
<td>25</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>C (n = 68)</td>
<td>11</td>
<td>16</td>
<td>4</td>
</tr>
</tbody>
</table>

*Primary end points were observed in the 1st 48 h in 27% of patients. Data are expressed as number or percent of patients. Definitions of groups as in Table 1.

Discussion

In this prospective, single-blind, randomized trial of patients with unstable angina, a high dose of low molecular weight heparin plus aspirin was superior to either regular unfractionated heparin plus aspirin or aspirin alone in reducing the number of major and minor events.

The angiographic features of our patients merit some discussion. Globally 43% had three-vessel coronary disease and 11% had left main disease, in association with one- or two-vessel disease. These phenomena can influence the prognosis of unstable angina and could have affected our results. However, because the findings were equally distributed among patient groups, the significance of the differences is maintained.

Aspirin. There are important observations (16,17) supporting the concept that aspirin is an excellent antithrombotic drug during the early phase of this coronary syndrome. However, the rate of recurrence of ischemia in the patients in our study receiving aspirin was still very high. Vascular thrombi may be resistant to aspirin for a variety of reasons. Disrupted atherosomatous lesions activate platelets by means of thrombin, an aspirin-independent agonist. Thrombin located in thrombi is protected from inactivation by heparin and aspirin because it is present in a configuration capable of proteolytically activating platelets and cleaving fibrinogen but is inaccessible to heparin (18).

In most previous trials the choice of aspirin dose was empiric. For example, in the RISC study (4) the dose was 75 mg/day, in the Veterans Administration Cooperative Study (19) it was 324 mg/day and in the study of Théroux et al. (20) it was 325 mg twice daily. Although increasing the dose of aspirin may influence other components of interactions between platelets and endothelium, larger doses have other potentially deleterious effects (21).

In the study of Théroux et al. (20) the prevalence of three-vessel disease was much less than that in our study. Thus, our patients had less favorable anatomy, perhaps making our findings even more significant. In fact, treatment for patients with unstable angina should consider the use of different doses, taking into account the different risk factors in this group. Our data show that 200 mg/day of aspirin is less effective than 200 mg/day combined with low molecular weight heparin.

Heparin. The usefulness of heparin in acute angina has been documented for >10 years (22). We thought that the

Table 4. Primary End Points*

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Events</th>
<th>Recurrent Angina</th>
<th>Major Bleeding</th>
<th>AMI</th>
<th>Revascularization Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>P Value</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>A (n = 73)</td>
<td>43</td>
<td>59</td>
<td>0.00001†</td>
<td>27</td>
<td>37</td>
</tr>
<tr>
<td>B (n = 70)</td>
<td>44</td>
<td>63</td>
<td>0.00001‡</td>
<td>31</td>
<td>44</td>
</tr>
<tr>
<td>C (n = 68)</td>
<td>15</td>
<td>22</td>
<td>--</td>
<td>14</td>
<td>21</td>
</tr>
</tbody>
</table>

*No deaths occurred in any group. †Difference between groups C and A. ‡Difference between groups A and B. §Difference between groups C and B. ‖Difference between groups B and A. Data are expressed as number or percent of patients. Definitions of groups and abbreviation as in Table 1.
the vast majority of events occurred within the 1st 48 h in all groups. Intravenous heparin is associated with many difficulties including the loss of heparin effect and maintenance of the therapeutic ranges (23-25). The GUSTO study (26) also recently demonstrated the frequency with which heparin falls to a subtherapeutic range as reflected by activated partial thromboplastin time times. In our study we decided to use a weight-adjusted nomogram of infusion to achieve optimal therapeutic ranges in the search for better results. Heparin is also affected by various substances. Platelet products, such as antiheparin factor (PF-4) (27), may interfere with heparin, as do vitronectin (28), fibronectin, lipoproteins (29) and vascular surfaces (30). There is evidence (31) that aggregation could be induced under certain conditions by using heparin with high molecular weight.

**Low molecular weight heparin.** Low molecular weight heparin is characterized by a specific anti-Factor Xa effect, inducing only a small prolongation of the general clotting test, such as activated partial thromboplastin time, prothrombin time and antithrombin activity when a high dose is used (32). Low molecular weight heparin and regular heparin have many common properties. It would be reasonable to assume that other reasons may explain these results:

1) It is known that low molecular weight heparin has a much lower affinity for plasma and matrix proteins, a demonstrated superior bioavailability and a longer half-life (33) than regular heparin, and it can be administered without laboratory monitoring (34).

2) Unfractionated heparin has a delay until the target activated partial thromboplastin time is reached.

3) Because this is a combination of two antithrombotic drugs, there may exist pharmacologic interactions not described at the moment.

**Limitations of this study.** Although this study demonstrated the safety of low molecular weight heparin in patients with unstable angina, because some principal outcomes may be subjective, a very important limitation of this trial is its single-blind nature.

The originally projected sample size of the trial was 315 patients to obtain a significant reduction of events. After 180 patients had been included, the Data Review Board Committee of the investigation performed an interim analysis that revealed an unexpected significant reduction of ischemic events (more than the initial 25% expected in the low molecular weight arm) in group C and significantly more bleeding complications in group B. The termination of the study on the basis of this analysis could be considered another important limitation.

This study also provided an opportunity to evaluate the total ischemic burden as defined by the occurrence of silent myocardial ischemia during the initial 48 h after admission for unstable angina. Multivariate analyses in previous studies showed that the presence of silent ischemia was a predictor of subsequent major ischemic events (35,36). Recently, the Advisory Groups of the Council for Myocardial Ischemia and Infarction (37) listed several ongoing studies of silent ischemia. Most of them (38-40) examine the use of treatment with beta-blockers, calcium channel antagonists or a combination of these agents.

We (6) previously demonstrated that the active thrombotic and thrombolytic process in silent ischemia within the framework of unstable angina, also confirmed by earlier reports of others (41), is more than a vasoconstrictive phenomenon or an imbalance between demand and supply of blood to the heart. In this study, low molecular weight heparin plus aspirin was at least superior to aspirin or aspirin plus regular heparin in reducing the number of major and minor ischemic events after the development of silent ischemia, including bleeding risk.

Other prospective evaluations (42-44) of stronger antithrombotic therapies with direct antithrombins or anti-IIb/IIIa glycoproteins—such as hirudin and monoclonal antibody, known as 7E3—are ongoing, but serious bleeding complications are being seen. Therefore, low molecular weight heparin appears to be an important alternative to test.
We are indebted to Elliot Rapaport, MD and Adolph Hutter, Jr., MD for reviewing the manuscript.

References


