Low Molecular Weight Heparin in Prevention of Restenosis After Angioplasty
Results of Enoxaparin Restenosis (ERA) Trial

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Background Heparin, an anticoagulant, possesses anti-proliferative effects and has been shown to reduce neointimal proliferation and restenosis following vascular injury in experimental studies.

Methods and Results The primary aim of this double-blind multicenter study was to determine if 40 mg Enoxaparin, a low molecular weight heparin, administered subcutaneously once daily for 1 month after successful angioplasty would reduce the incidence of restenosis. Four hundred fifty-eight patients were randomized at nine clinical centers (231 to placebo and 227 to Enoxaparin). The primary end point was angiographic or clinical restenosis. Angiographic restenosis was defined as a loss of 50% of the initial gain as measured by quantitative coronary angiography (QCA) at a core laboratory. In the absence of QCA, clinical evidence of restenosis was defined as death, myocardial infarction, repeat revascularization, or worsening angina. Using the intention-to-treat analysis for all patients, restenosis occurred in 51% of the placebo group and 52% of the Enoxaparin group (relative risk, 1.07, P=.625). Likewise, no difference in restenosis was evident when the change in minimal lumen diameter or other angiographic definitions of restenosis were used. Adverse clinical events were infrequent and did not differ between the groups with the exception of minor bleeding complications, which were more common in the Enoxaparin group.

Conclusions Enoxaparin (40 mg/d SC for 1 month) following successful angioplasty did not reduce the incidence of angiographic restenosis or the occurrence of clinical events over 6 months. The treatment was well tolerated, although in-hospital minor bleeding was more common with active treatment. (Circulation. 1994;90:908-914.)

Key Words • heparin • restenosis • angioplasty • clinical trials

Coronary angioplasty is estimated to have been performed in more than 300 000 patients in 1991.1 Since its inception, the success of the procedure has steadily improved, and the incidence of short-term complications has decreased.2 However, the long-term outcome has continued to be complicated by restenosis. Angiographic evidence of restenosis occurs in 30% to 50% of patients after a successful procedure and necessitates a repeat procedure in 20% to 25% of patients.3

Experimental studies suggest that restenosis is a physiological response to severe vascular injury and is analogous to the process of generalized wound healing.4 Angioplasty stretches the vascular wall, often tearing the neointimal plaque.5 Immediately after dilatation, elastic recoil occurs with subsequent deposition of platelets and formation of thrombus.6 Smooth muscle cell proliferation and matrix formation repair the damaged vessel, resulting in a final remodeling of the lumen. In an effort to reduce the incidence of restenosis, a number of drugs have been evaluated, including antiplatelets, antithrombotics, calcium antagonists, omega-3 fatty acids, angiotensin-con-verting enzyme inhibitors, steroids, and anti-inflammatory drugs.7 To date, no agent has been shown to be effective in preventing this process.

Heparin has pharmacological properties that are potentially useful in reducing restenosis. Not only does it have anticoagulant and antithrombotic effects, but it has also been shown to prevent neointimal proliferation in vitro as well as in animal models of vascular injury.8-20 Enoxaparin is a low molecular weight heparin (approximately 4500 d) obtained by partial and controlled depolymerization of a benzyl ester of porcine mucosal heparin.21 Compared with heparin, Enoxaparin provides approximately three times greater anti-Xa activity than anti-IIa activity. It also has a significantly longer half-life and has proven to be effective in the prevention of deep vein thrombophlebitis when given subcutaneously once or twice daily.22-24 The purpose of this multicenter trial was to evaluate whether Enoxaparin given subcutaneously daily for 28 days after successful angioplasty would reduce the incidence of restenosis as determined by angiography and by the occurrence of clinical signs and symptoms.

Methods

All patients at nine clinical centers were screened for eligibility between May 1989 and August 1990. Patients were considered if they were 21 years of age or older and had a successful angioplasty performed. A successful procedure was defined as a >50% stenosis reduced to <50% stenosis with a ≥20% change in diameter. Measurements were made using hand-held calipers by the principal investigator or his designee at each clinical center. Patients were excluded if they met one

Received January 27, 1994; revision accepted April 18, 1994.
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of the following criteria: woman of childbearing potential, history of bleeding disorders or recent active bleeding, uncontrolled asthma or hypertension (blood pressure >180/105 mm Hg), active peptic ulcer disease, history of heparin-associated thrombocytopenia, acute myocardial infarction within 5 days, abrupt vessel closure after angioplasty, or other complications requiring heparin therapy for >24 hours after percutaneous transluminal coronary angioplasty (PTCA). A left main artery stenosis of >50%, angioplasty of a saphenous vein graft, or prior PTCA at the same site also were exclusion criteria. The PTCA was performed using standardized techniques as previously reported. Angiography before and immediately after angioplasty was performed after intracoronary nitroglycerin administration. The two orthogonal views that best identified the lesions were considered for subsequent quantitative coronary analysis at a core laboratory.

Patients meeting qualifying criteria were approached for informed consent before PTCA and were randomized to receive either placebo or Enoxaparin (40 mg SC daily for 28 days) after a successful procedure. The drug was begun 2 hours after femoral sheath removal and was administered no later than 24 hours after the procedure. Heparin was administered during the PTCA procedure and adjusted to maintain the activated clotting time at >300 seconds. Acetylsalicylic acid (325 mg PO QD) was administered 1 day before and throughout the treatment period. Patients were instructed in subcutaneous administration of the study drug by a trained study nurse at each clinical site. Calcium antagonists were administered before and after PTCA but were discontinued unless considered clinically necessary by the investigator. In general, patients were discharged from the hospital 1 or 2 days after angioplasty.

Patients returned at 1, 4, and 24 weeks after angioplasty for clinical and bleeding assessment. Laboratory assessment measured at each time point included complete blood count, coagulation profile, and liver function tests. A treadmill exercise test using the modified Bruce protocol was obtained before and at 1 and 24 weeks after randomization. ST-segment changes and exercise duration were recorded. All patients returned for repeat coronary angiography 24-54 weeks after randomization. Angiography was again performed using 7F or 8F catheters after administration of intracoronary or intravenous nitroglycerin. The two optimal orthogonal views previously identified to best demonstrate the stenosis were repeated.

The angiograms were sent to the core angiographic laboratory at Baylor College of Medicine. Each film was viewed by a trained technician who was blinded to patients' therapy. Each projection optimally demonstrating the target lesion was identified. The pre-PTCA, post-PTCA, and follow-up angiograms were analyzed using the Coronary Angiographic Analysis System (CAAS) as previously described.24-26 The stenosis and proximal and distal segments were manually identified and then digitized using a semiautomated edge-detection system. Two views were used when possible, and the minimal lumen diameter, percent area stenosis, and reference diameters were calculated. Ten percent of the angiograms were rereviewed in a blinded fashion as part of a quality control assessment. All films demonstrating >0.2-mm difference in reference diameter were reanalyzed, and the lesion was redetermined. The average of all diluted lesions for that patient was used in the analysis. Other angiographic data, including ejection fraction, number of vessels diseased, and morphology, were determined by the investigators at each clinical site.

Clinical assessment included the occurrence of death, myocardial infarction, emergency or elective bypass surgery, emergency or elective PTCA, unstable angina, occurrence of angina, or worsening of angina on effort by two or more grades as defined by Canadian Cardiovascular Society anginal classifica-

### TABLE 1. Patient Analysis Groups

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Patients Receiving Placebo, n (%)</th>
<th>Patients Receiving Enoxaparin, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>231</td>
<td>228</td>
<td>459</td>
</tr>
<tr>
<td>Not treated</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>All treated</td>
<td>231 (100%)</td>
<td>227 (&gt;99%)</td>
<td>458 (&gt;99)</td>
</tr>
<tr>
<td>Evaluable</td>
<td>176 (76%)</td>
<td>181 (79%)</td>
<td>357 (78%)</td>
</tr>
</tbody>
</table>

In addition, bleeding was assessed and quantified as major or minor. Major bleeding was defined as a clinically evident bleeding episode associated with a decrease in hematoglobin of at least 2 g/dL and/or requiring transfusion of at least 2 U of blood. Any intracerebral or retroperitoneal bleed was considered a major bleed. The site and source of bleeding episodes were noted.

The primary end point of the trial was a loss of 50% of the initial gain in lumen diameter achieved at angioplasty or clinical evidence of restenosis. This angiographic definition is also known as the National Heart, Lung, and Blood Institute (NHLBI) IV PTCA definition.3 In the absence of angioplasty, clinical evidence of restenosis was defined as death, myocardial infarction, repeat revascularization, or worsening angina. Other angiographic categorical definitions of restenosis as well as the change in minimal lumen diameter were also analyzed.3 Additional efficacy assessment included the presence of >0.1 mV of ST-segment depression and exercise duration on the exercise stress test and clinical events including worsening angina, death, myocardial infarction, bypass surgery, and angioplasty.

### Statistical Analysis

The primary analysis of efficacy used the intention-to-treat principle. The demographic variables were compared, but statistical analyses were not performed. For the efficacy analysis, justification for pooling across centers was investigated using a two-way logistical regression model (PROC CATMOD) with factors for treatment group, center, and treatment by center investigated. Treatment comparisons were based on a .05 significance level, the odds ratio of treatment failure was computed, and the 95% confidence intervals were determined. The incidence of treatment failure in the subgroups was also calculated. The change in minimal lumen diameter was analyzed as a continuous variable. For patients who had more than one lesion dilated, the average minimal lumen diameter of all lesions successfully diluted was used for this analysis. A weighted analysis for mean change in minimal lumen diameter of a lesion was also performed.

### Results

#### Patient Analysis Groups

The all-treated patient group included all patients who received at least one dose of the study medication (Table 1). The “evaluable” patient group included all treated patients who also had angiography performed at 26±2 weeks after randomization or earlier if warranted by recurrence of angina or clinical symptoms and had study medication administered within 36 hours of successful PTCA and had received a minimum of 22 doses.

#### Baseline Characteristics

The baseline demographic characteristics of all treated patients are given in Tables 2 and 3. Two hundred thirty-one patients were randomized to receive placebo and 227 patients to receive Enoxaparin. The two groups did not differ in any baseline clinical or angiographic characteristic. In general, the patients had multivessel
disease with complex lesion characteristics (as defined by American Heart Association lesion classification). A single lesion was dilated in >60% of patients despite the presence of multivessel disease in the majority. Comparison of baseline characteristics in the evaluable patient group also showed no differences between treatment groups in any baseline characteristic.

Table 3. Baseline Angiographic Characteristics of All Treated Patients

<table>
<thead>
<tr>
<th>No. of vessels</th>
<th>Patients Receiving Placebo, n (%)</th>
<th>Patients Receiving Enoxaparin, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>115 (50)</td>
<td>110 (48)</td>
<td>225 (49)</td>
</tr>
<tr>
<td>Two</td>
<td>80 (35)</td>
<td>73 (32)</td>
<td>153 (33)</td>
</tr>
<tr>
<td>Three</td>
<td>36 (15)</td>
<td>45 (20)</td>
<td>81 (18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of lesions dilated</th>
<th>Patients Receiving Placebo, n (%)</th>
<th>Patients Receiving Enoxaparin, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>159 (69)</td>
<td>176 (78)</td>
<td>325 (73)</td>
</tr>
<tr>
<td>More than one</td>
<td>70 (30)</td>
<td>50 (22)</td>
<td>120 (26)</td>
</tr>
</tbody>
</table>

| Percent stenosis (QCA) | 70.6±12.2 | 72.5±11.3 | 71.5±11.8 |
| ACC/AHA lesion class27 | A 128 (40) | 117 (40) | 245 (40) |
|                        | B 179 (56) | 157 (54) | 336 (55) |
|                        | C 11 (3)   | 16 (6)   | 27 (4)   |
|                        | Unknown 2 (1) | 1 (1) | 3 (1) |

Ejection fraction, % 59.2 60.1 59.6

QCA indicates quantitative coronary angiography; ACC, American College of Cardiology; and AHA, American Heart Association.

Table 4. Reasons for Discontinuation From Study

<table>
<thead>
<tr>
<th>Reason</th>
<th>Patients Receiving Placebo, n (%)</th>
<th>Patients Receiving Enoxaparin, n (%)</th>
<th>Overall, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>20 (9)</td>
<td>15 (7)</td>
<td>35 (8)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>13 (6)</td>
<td>10 (4)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Did not meet entry criteria</td>
<td>3 (2)</td>
<td>1 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (4)</td>
<td>13 (5)</td>
<td>24 (6)</td>
</tr>
</tbody>
</table>

Total 51 (22) 43 (19) 94 (20)

Fifty-one patients in the placebo group and 43 patients in the Enoxaparin group were discontinued from the study. The primary reason for discontinuation was the occurrence of an adverse event. In addition, 13 placebo and 10 Enoxaparin patients were lost to follow-up, and a small percentage of patients did not meet entry criteria (Table 4). Six placebo and three Enoxaparin patients did not have an analyzable follow-up angiogram.

Primary Efficacy Analysis

With the intention-to-treat analysis, treatment failures in the all-treated group were 51% for placebo patients and 52% for Enoxaparin patients (P = .625) (Fig 1). Treatment failure was defined as a loss of 50% of the gain in lumen diameter achieved at angioplasty or, in the absence of quantitative angiography, clinical evidence of restenosis defined as death or the occurrence of myocardial infarction, need for bypass surgery, unstable angina, or worsening or new angina.

A similar analysis was done in the evaluable patient group (quantitative coronary angiography was available, and patients were compliant with any drug administration). Restenosis occurred in 49% of the placebo group and 50% of the Enoxaparin group (odds ratio, 1.04; P > .05; 95% confidence limit, 0.73). Within the evaluable patient group, the incidence of restenosis was compared in the following subsets: sex, age, race, anginal class, cholesterol level, patients with a myocardial infarction within 28 days, prior thrombolytic therapy,
patients with initially positive exercise test, or single-
lesion PTCA. No differences were seen between treated
and placebo patient groups in these subgroups.

Angiographic Restenosis

The change in minimal lumen diameter and reference
diameter—before PTCA, after PTCA, and at follow-
up—is shown in Table 5 for all lesions in the evaluable
patients for whom follow-up angiography was available.
The acute gain in minimal lumen diameter was 1.10 mm
for the placebo group and 1.15 mm for the Enoxaparin
group. The late loss in lumen diameter was 0.49 mm and
0.54 mm, respectively ($P=.78$). The cumulative distribu-
tion of the minimal lumen diameter before PTCA,
immediately after PTCA, and at follow-up similarly
showed no differences between groups (Figs 2 and 3)
and followed a gaussian distribution as has been re-
ported by others. Likewise, analysis of incidence of
angiographic restenosis by lesion for all patients with a
follow-up angiogram is given in Table 6. The five
commonly used categorical definitions also showed no
differences. Other postprocedural characteristics, in-
cluding dissection, were not different, although few
dissections were present as a result of the strict entry
inclusion and exclusion criteria.

Clinical Outcome

As shown in Table 7, serious adverse outcomes were
rare, with death, myocardial infarction, and emergency
bypass surgery occurring in five placebo patients and
eight Enoxaparin patients. The most common event was
the presence of asymptomatic angiographic restenosis
using the NHLBI IV definition. Asymptomatic angio-
graphic restenosis occurred in 29% of the placebo group
and 27% of the Enoxaparin group. Of interest is that
only 17% of the placebo group and 16% of the Enox-
aparin group developed significant angina, suggesting
that a sizable percentage of the patients had silent
restenosis. Subsequent revascularization with bypass
surgery or angioplasty was infrequent (9% of the pla-
cebo group and 12% of the Enoxaparin group) and
probably is due to the low incidence of angina in both
patient groups. However, this incidence of revascu-
larization may also be artificially low as the performance
of angioplasty or surgery was not recorded after comple-
tion of 24 weeks of follow-up.

Exercise testing using the modified Bruce protocol at
both 1 week and follow-up was performed in 205
placebo and 205 Enoxaparin patients. Analyzable mod-
ified Bruce protocol exercise tests were not consistently
obtained at each time point, making comparisons be-
tween groups difficult. A comparison of the 109 patients
in the placebo group and the 106 patients in the
Enoxaparin group in whom adequate paired exercise
tests were obtained showed no differences in anginal
ST-segment changes. Seventeen percent of the placebo
group and 12% of the Enoxaparin group developed
exercise-induced angina at follow-up, whereas 20% and
24%, respectively, developed new ST-segment depres-
sions at the 24-week exercise test. Again, these data may
be skewed as patients who developed clinical evidence
of restenosis earlier during follow-up did not have a
24-week exercise test.

Bleeding Complications

The overall incidence of major and minor bleeding
was 34% in the placebo group and 48% in the Enox-

Table 5. Quantitative Angiographic Results for All Treated Patients

<table>
<thead>
<tr>
<th>Study Period</th>
<th>No Lesions</th>
<th>Reference Diameter, mm</th>
<th>MLD, mm</th>
<th>No Lesions</th>
<th>Reference Diameter, mm</th>
<th>MLD, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before angioplasty</td>
<td>235</td>
<td>2.84</td>
<td>0.84</td>
<td>227</td>
<td>2.87</td>
<td>0.81</td>
</tr>
<tr>
<td>After angioplasty</td>
<td>235</td>
<td>2.87</td>
<td>1.94</td>
<td>227</td>
<td>2.89</td>
<td>1.96</td>
</tr>
<tr>
<td>Follow-up</td>
<td>235</td>
<td>2.76</td>
<td>1.45</td>
<td>227</td>
<td>2.96</td>
<td>1.43</td>
</tr>
</tbody>
</table>

Initial gain: 1.10
Late loss: -0.49

MLD indicates minimal lumen diameter.

Fig 2. Plot of minimal lumen diameter (MLD) measured by quantitative coronary angiography before angioplasty (PTCA), after PTCA, and at follow-up is shown for all patients who had an evaluable end point angiogram. No differences were seen between the Enoxaparin and control groups.
Apiforphin group (P<.0008). This difference primarily was confined to minor bleeding episodes. There were no episodes of intracerebral or retroperitoneal bleeding, and all except one major bleed occurred at the femoral arterial entry site. Nearly all major and minor groin bleeding occurred during the initial hospital stay.

Other adverse events were infrequent and did not differ between groups. Of importance, platelet count, liver function tests, prothrombin time, and partial thromboplastin time as well as cholesterol levels were not significantly different.

**Discussion**

The results of the present study demonstrate that Enoxaparin, a low molecular weight heparin, given for 28 days after angioplasty did not reduce the incidence of restenosis or reduce adverse clinical outcomes when compared with placebo. It did, however, result in an increase in bleeding complications. These complications were usually minor, occurred at the arterial entry site during the initial hospitalization, and were easily managed by usual medical methods.

Restenosis is a multifactorial process that involves elastic recoil, platelet deposition, thrombus formation, inflammation, smooth muscle cell proliferation, and matrix organization. Heparin is used routinely during angioplasty to prevent a thrombotic abrupt vessel closure. However, it is also recognized to have antiproliferative actions that may be useful in preventing restenosis.

Heparin was initially isolated from porcine mucosa and was shown to have anticoagulant and antithrombotic properties. The mechanism of this action was later demonstrated to be dependent on binding to antithrombin III, resulting in a conformational change that allows antithrombin III to bind avidly with factors IIa and Xa. Heparin is a sulfonated glycosaminoglycan and is a mixture of chain lengths that results in molecular weights ranging from 5000 to 50 000 d. In 1977, Clowes and Karkovsky demonstrated that heparin inhibited neointimal proliferation in a rat injury model. Subsequently, a number of studies have shown that heparin can reduce experimental intimal hyperplasia by 30% to 60%. Cell culture studies have demonstrated that the antiproliferative properties are greater for the lower molecular weight heparins and are independent of its ability to bind antithrombin III. Thus, the nonanticoagulant fractions are as effective as the anticoagulant fractions in prevention of neointimal proliferation. The antiproliferative effect is dose dependent. Although the exact mechanism of action of heparin in preventing cell proliferation is not known, heparin and its analogues appear to block the cell cycle at the G stage. Incorporation into the cell nucleus appears to be important in its antiproliferative actions. In addition, heparin can bind and alter growth factor activity. A related form of heparin, heparan sulfate is a naturally

**Table 6. Incidence of AngiographicRestenosis Perfusion for All Patients With a Follow-up Angiogram**

<table>
<thead>
<tr>
<th>Definition*</th>
<th>Patients Receiving Placebo, n (%)</th>
<th>Patients Receiving Enoxaparin, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>192 (30)</td>
<td>202 (32)</td>
</tr>
<tr>
<td>NHLBI I (≥30% increase)</td>
<td>57 (30)</td>
<td>65 (32)</td>
</tr>
<tr>
<td>NHLBI II (&lt;50% to &gt;70%)</td>
<td>33 (17)</td>
<td>44 (21)</td>
</tr>
<tr>
<td>NHLBI III (≤10% before stenosis)</td>
<td>40 (21)</td>
<td>44 (21)</td>
</tr>
<tr>
<td>NHLBI IV (loss 50% gain)</td>
<td>97 (51)</td>
<td>106 (52)</td>
</tr>
<tr>
<td>&lt;50% to &gt;50%</td>
<td>86 (45)</td>
<td>87 (43)</td>
</tr>
</tbody>
</table>

NHLBI indicates National Heart, Lung, and Blood Institute.

*Angiographic definitions of restenosis are provided in Reference 3.

**Table 7. Adverse Clinical Outcomes for All Treated Patients**

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Patients Receiving Placebo, n (%)</th>
<th>Patients Receiving Enoxaparin, n (%)</th>
<th>Overall, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>MI</td>
<td>4 (2)</td>
<td>5 (2)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Elective CABG</td>
<td>2 (1)</td>
<td>2 (&lt;1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Emergency PTCA</td>
<td>5 (3)</td>
<td>7 (3)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Elective PTCA</td>
<td>10 (5)</td>
<td>17 (8)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>4 (2)</td>
<td>1 (&lt;1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Occurrence or worsening of angina</td>
<td>33 (17)</td>
<td>33 (16)</td>
<td>66 (17)</td>
</tr>
<tr>
<td>Asymptomatic restenosis</td>
<td>56 (29)</td>
<td>54 (27)</td>
<td>110 (28)</td>
</tr>
<tr>
<td>No evidence of restenosis</td>
<td>77 (40)</td>
<td>81 (40)</td>
<td>188 (40)</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; CABG, emergency coronary artery bypass surgery; and PTCA, percutaneous transluminal coronary angioplasty.
occurring glycosaminoglycan that is a constituent of the extracellular matrix of the arterial wall.\textsuperscript{16} It is believed that this compound may provide an important cell regulatory action within the arterial wall.

Enoxaparin, a low molecular weight heparin, differs from regular heparin in a number of ways.\textsuperscript{21} It is generated from heparin by chemical depolymerization and has an average molecular weight of 4500 d. Due to the shorter chain length, it has approximately three times more anti-Xa activity than anti-IIa activity in contrast to the 1:1 ratio for heparin. Importantly, its half-life as measured by anti-Xa activity is 4.6 hours compared with 2.95 hours for heparin; however, anti-Xa activity can be measured for as long as 24 hours after a single dose.\textsuperscript{22} Experimental studies using a hypercholesterolemic rabbit model have demonstrated a dose-dependent reduction in restenosis using Enoxaparin once daily.\textsuperscript{20}

The present study represents the first report of the sustained use of a low molecular weight heparin to prevent restenosis in humans. Ellis et al\textsuperscript{29} reported that an 18- to 24-hour infusion of heparin immediately after PTCA did not prevent restenosis in a randomized trial of 416 patients. Three brief reports of heparin in restenosis have been published.\textsuperscript{30-33} In one study using Fragmin, a low molecular weight heparin, a significant trend toward a reduction in restenosis was seen.\textsuperscript{31} A preliminary brief report of a randomized trial of 10 000 U heparin SC once daily compared with placebo was prematurely discontinued because of a high incidence of adverse events and angiographic restenosis.\textsuperscript{29} One potential explanation for the high incidence of treatment failure seen in this trial may be the drug-dosing regimen. Because 10 000 U heparin SC was given daily, it is possible that a heparin rebound may have occurred. As reported in this trial, no significant increase in adverse events or restenosis was documented with the use of subcutaneous low molecular weight heparin. This may well be due to lack of rebound because of its longer half-life. Two other large trials using low molecular heparin are under way (FACT and EMPAR trials).

### Study Limitations

There are a number of study limitations. The lack of an effect on restenosis in this trial does not exclude the possibility that Enoxaparin prevents restenosis in humans. In our study, we chose to begin Enoxaparin after angioplasty. Experimental studies have shown that pretreatment can significantly increase the effectiveness of heparin as an antiproliferative agent.\textsuperscript{34} We chose to start the drug after PTCA for several reasons. Experimental studies have shown that heparin is effective even if administered after injury.\textsuperscript{16} In addition, pretreatment could increase the risk of periprocedural bleeding. An additional limitation is the low dose of heparin given in this study. The antiproliferative effect of heparin is well documented to be dose dependent.,\textsuperscript{3-20,34} and the relation between heparin's anti-Xa activity and proliferation is uncertain. Although direct extrapolation of doses between studies in animals and humans is hazardous, prior animal studies suggest that extremely high doses were necessary to achieve the desired effect. The doses used in this trial were the highest previously studied doses that have been shown to be safe and effective in the prevention of deep vein thrombophlebitis in patients undergoing high-risk orthopedic surgery.\textsuperscript{22} Although higher doses may have been effective, concerns about safety precluded using doses equal to those studied experimentally. Finally, the duration of therapy (28 days) may not have been sufficient. However, experimental studies suggest that therapy need be given only during the proliferative phase, which is estimated to extend to the first few weeks after injury.\textsuperscript{16} It is possible, however, that proliferation occurs beyond this time point and that a longer duration of therapy may have been necessary to reduce restenosis. Many of these limitations are being addressed in other current clinical trials of heparin and low molecular weight heparin in the prevention of restenosis. Finally, it is possible that mechanisms other than intimal hyperplasia are important in restenosis. Experimental studies and intravascular ultrasound studies in humans suggest that late remodeling may be more important than intimal hyperplasia in causing restenosis.\textsuperscript{34,35}

### Table 8. Bleeding Complications, Thrombocytopenia, and Injection Site Hemorrhage for All Treated Patients

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Patients Receiving Placebo, n (%)</th>
<th>Patients Receiving Enoxaparin, n (%)</th>
<th>P</th>
<th>Overall, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed*</td>
<td>3 (1)</td>
<td>10 (4)</td>
<td>.055</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Minor bleed</td>
<td>78 (33)</td>
<td>98 (43)</td>
<td>.01</td>
<td>174 (38)</td>
</tr>
<tr>
<td>Groin</td>
<td>67</td>
<td>94</td>
<td></td>
<td>161 (35)</td>
</tr>
<tr>
<td>Nasal</td>
<td>3</td>
<td>0</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2</td>
<td>2</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (3)</td>
<td>9 (4)</td>
<td></td>
<td>16 (3)</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>13 (6)</td>
<td>35 (15)</td>
<td>&lt;.001</td>
<td>48 (21)</td>
</tr>
<tr>
<td>Decrease in hemoglobin &gt; 2 g/dL</td>
<td>16 (7)</td>
<td>21 (9)</td>
<td></td>
<td>37 (8)</td>
</tr>
</tbody>
</table>

* Major bleed was bleeding resulting in death, clinically overt with a decrease in hemoglobin of ≥2 g/dL, or a transfusion of ≥2 U red blood cells or was retroperitoneal or intracranial.
Heparin and related compounds, such as Enoxaparin, possess anticoagulant and antiproliferative effects that make them attractive therapeutic agents for the prevention of restenosis. Although this study demonstrates no effect on the prevention of restenosis, further study is warranted. High-dose, local delivery or combination therapy with other agents may be needed to inhibit this complex process.

Acknowledgment

This work was supported by Rhône-Poulenc Rorer.

Appendix

Enoxaparin Investigators

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_Circulation_. 1994;90:908-914
doi: 10.1161/01.CIR.90.2.908

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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