ORIGINAL ARTICLE

Enoxaparin versus Unfractionated Heparin in Elective Percutaneous Coronary Intervention

Gilles Montalescot, M.D., Ph.D., Harvey D. White, M.B., Ch.B., D.Sc., Richard Gallo, M.D., Marc Cohen, M.D., P. Gabriel Steg, M.D., Philip E.G. Aylward, M.B., Ch.B., Ph.D., Christoph Bode, M.D., Ph.D., Massimo Chiariello, M.D., Spencer B. King III, M.D., Robert A. Harrington, M.D., Walter J. Desmet, M.D., Carlos Macaya, M.D., Ph.D., and Steven R. Steinhubl, M.D., for the STEEPLE Investigators*

ABSTRACT

BACKGROUND

Despite its limitations, unfractionated heparin has been the standard anticoagulant used during percutaneous coronary intervention (PCI). Several small studies have suggested that intravenous enoxaparin may be a safe and effective alternative. Our primary aim was to assess the safety of enoxaparin as compared with that of unfractionated heparin in elective PCI.

METHODS

In this prospective, open-label, multicenter, randomized trial, we randomly assigned 3528 patients with PCI to receive enoxaparin (0.5 or 0.75 mg per kilogram of body weight) or unfractionated heparin adjusted for activated clotting time, stratified according to the use or nonuse of glycoprotein IIb/IIIa inhibitors. The primary end point was the incidence of major or minor bleeding that was not related to coronary-artery bypass grafting. The main secondary end point was the percentage of patients in whom the target anticoagulation levels were reached.

RESULTS

Enoxaparin at a dose of 0.5 mg per kilogram was associated with a significant reduction in the rate of non–CABG-related bleeding in the first 48 hours, as compared with unfractionated heparin (5.9% vs. 8.5%; absolute difference, –2.6; 95% confidence interval [CI], –4.7 to –0.6; P=0.01), but the higher enoxaparin dose was not (6.5% vs. 8.5%; absolute difference, –2.0; 95% CI, –4.0 to 0.0; P=0.051). The incidence of major bleeding was significantly reduced in both enoxaparin groups, as compared with the unfractionated heparin group. Target anticoagulation levels were reached in significantly more patients who received enoxaparin (0.5-mg-per-kilogram dose, 79%; 0.75-mg-per-kilogram dose, 92%) than who received unfractionated heparin (20%, P<0.001).

CONCLUSIONS

In elective PCI, a single intravenous bolus of 0.5 mg of enoxaparin per kilogram is associated with reduced rates of bleeding, and a dose of 0.75 mg per kilogram yields rates similar to those for unfractionated heparin, with more predictable anticoagulation levels. The trial was not large enough to provide a definitive comparison of efficacy in the prevention of ischemic events. (ClinicalTrials.gov number, NCT00077844.)

From Institut de Cardiologie, Centre Hospitalier Universitaire Pitié–Salpêtrière, Paris (G.M.); the Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand (H.D.W.); the Montreal Heart Institute, Université de Montréal, Montreal (R.G.); the Division of Cardiology, Newark Beth Israel Medical Center, Newark, NJ (M.C.); the Service de Cardiologie, Hôpital Bichat, Paris (P.G.S.); Department of Cardiology, Flinders Medical Center, Adelaide, SA, Australia (P.E.G.A.); Abteilung Innere Medizin III, Universitätsklinikum Freiburg, Freiburg, Germany (C.B.); the Division of Cardiology, Federico 2nd University, Naples, Italy (M.C.); Fuqua Heart Center of Atlanta at Piedmont Hospital, Atlanta (S.B.K.); the Division of Cardiology, Duke University Medical Center, Durham, NC (R.A.H.); University Hospital Gasthuisberg, Leuven, Belgium (W.J.D.); Servicio de Cardiología, Hospital Universitario, Madrid (C.M.); and the Division of Cardiology, University of Kentucky, Lexington (S.R.S.). Address reprint requests to Dr. Montalescot at Institut de Cardiologie, Bureau 2-236, Centre Hospitalier Universitaire Pitié–Salpêtrière, 47 Boulevard de l'Hôpital, 75013 Paris, France, or at gilles.montalescot@psl.aphp.fr.

*Participants in the Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation (STEEPLE) trial are listed in the Appendix.

N Engl J Med 2006;355:1006-17.

THE AMERICAN COLLEGE OF CARDIOLOGY, the American Heart Association, and the European Society of Cardiology recommend the use of intravenous unfractionated heparin, with the dose adjusted for the activated clotting time, during percutaneous coronary intervention (PCI).[1,2] However, better anticoagulation regimens are needed for PCI, given the limitations of unfractionated heparin, which include its sometimes difficult-to-manage effects on coagulation, the need for repeated monitoring of coagulation, the narrow therapeutic window, the potential induction of platelet activation, and the risk of thrombocytopenia.[3]

The use of low-molecular-weight heparins as anticoagulants is increasing in patients with acute coronary syndrome who undergo PCI[4-6] and in those undergoing elective procedures.[7,8] As compared with unfractionated heparin, low-molecular-weight heparins are considered to induce a more stable and predictable anticoagulant dose response (obviating the necessity for coagulation monitoring), and to have a longer half-life and a greater ratio of anti–factor Xa activity to anti–factor IIa activity, which reduces the generation and activation of thrombin.[3,9] Low-molecular-weight heparins are also less apt to induce platelet activation, release of the von Willebrand factor, and inflammation.[10-13]

Small or noncomparative trials have evaluated a single intravenous bolus of enoxaparin — 1 mg,[14-18] 0.75 mg,[14,19-21] or 0.5 mg[7,22] per kilogram of body weight — in patients undergoing PCI with or without the administration of glycoprotein IIb/IIIa inhibitors. However, these uncontrolled studies have not allowed definite conclusions to be drawn about the efficacy of enoxaparin as compared with that of standard anticoagulation regimens involving unfractionated heparin. In a meta-analysis of data from randomized studies comparing intravenous low-molecular-weight heparins and intravenous unfractionated heparin in patients undergoing PCI, there was a nonsignificant trend toward a reduction in major bleeding with low-molecular-weight heparins and no difference between groups in the occurrence of ischemic events.[8] In an additional analysis, a dose of less than 1 mg of enoxaparin per kilogram resulted in fewer ischemic and bleeding events than a dose of 1 mg per kilogram.

We conducted a large-scale, randomized, controlled trial to evaluate whether the safety of intravenous low-molecular-weight heparins was superior to that of unfractionated heparin in patients undergoing elective PCI.

METHODS

The Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation (STEEPLE) trial was a prospective, open-label, parallel-group trial evaluating intravenous enoxaparin at a dose of 0.5 mg or 0.75 mg per kilogram, as compared with intravenous unfractionated heparin, in patients undergoing elective PCI.

The protocol was written by Dr. Montalescot and modified on the basis of discussions with the sponsor (Sanofi-Aventis) and the members of the steering committee (see the Appendix). The data were gathered by the sponsor and were maintained and analyzed by Altizem, a contract research organization. The steering committee vouches for the integrity and completeness of the data, and the statistician vouches for the accuracy of the data analysis. The publication committee prepared the manuscript with suggestions from the steering committee and the sponsor. The publication committee had final authority over the content of the manuscript.

PATIENTS

Patients were enrolled at 124 sites in nine countries. Patients were eligible for the study if they were older than 17 years of age, were scheduled to undergo elective PCI with a femoral approach, and did not meet any of the exclusion criteria: recent thrombolysis, a planned staged procedure, an increased risk of bleeding, treatment with a parenteral antithrombotic agent before PCI, or a known hypersensitivity to the drugs used in the study. The study was conducted according to the Declaration of Helsinki and local regulations. Approval for the trial was obtained from the institutional review board at each site. All patients gave written informed consent.

STUDY PROTOCOL

Eligible patients were randomly assigned to receive an intravenous bolus of unfractionated heparin, adjusted for activated clotting time according to current guidelines,[1] or intravenous enoxaparin at a dose of 0.5 or 0.75 mg per kilogram. We assigned

patients using an interactive voice-response system at the central randomization center. Random permuted blocks were used to make assignments in a 1:1:1 ratio that were stratified according to center and planned use of glycoprotein IIb/IIIa inhibitors (no or yes). All patients received aspirin (75 to 500 mg per day) and thienopyridines, according to local practice.

Patients who were assigned to either enoxaparin group received a single intravenous bolus of enoxaparin, without anticoagulation monitoring, after sheath insertion and immediately before PCI. The assigned dose was used regardless of whether a patient was also receiving the glycoprotein IIb/IIIa inhibitor. When procedures were prolonged by more than 2 hours, an additional bolus of enoxaparin (half the original dose) was recommended.[23]

Patients who were randomly assigned to receive unfractionated heparin and who were not receiving concurrent glycoprotein IIb/IIIa inhibitors were given an initial intravenous bolus of 70 to 100 IU per kilogram to achieve a target activated clotting time of 300 to 350 seconds. Patients who received concurrent glycoprotein IIb/IIIa inhibitors were given an initial bolus of 50 to 70 IU of unfractionated heparin per kilogram to achieve a target activated clotting time of 200 to 300 seconds. Additional boluses of unfractionated heparin were given before the PCI if the lower limit of the target activated clotting time was not reached. Unfractionated heparin was readministered during the procedure, at the discretion of the investigator, when measurements of activated clotting time dropped below the recommended range. In all centers, activated clotting time was measured with a standardized Hemochron device (ITC).

Arterial closure devices were permitted according to the practice at each institution. Sheath removal was authorized at an activated clotting time between 150 and 180 seconds in the unfractionated heparin group,[24] 4 to 6 hours after the end of the PCI in the group given 0.75 mg of enoxaparin per kilogram, and immediately after the end of the PCI in the group given 0.5 mg of enoxaparin per kilogram. No monitoring of anticoagulation was required before sheath removal in patients receiving enoxaparin.

END POINTS

The primary end point of the trial was the occurrence of major or minor bleeding not related to coronary-artery bypass grafting (CABG) during the first 48 hours after the index PCI, according to prespecified definitions (Table 1). The main secondary efficacy end point was the achievement of therapeutic anticoagulation at the beginning and end of PCI. Specifically, we compared the proportion of patients receiving enoxaparin in whom the target anti–factor Xa levels of 0.5 to 1.8 IU per milliliter (analyzed centrally) were achieved[25,26] with the proportion of patients receiving unfractionated heparin in whom the target activated clotting time (200 to 300 seconds with glycoprotein IIb/IIIa inhibitors or 300 to 350 seconds without)[1] was achieved, at the start and the end of PCI.

We also studied other secondary end points. The first was a composite of non–CABG-related major bleeding up to 48 hours after the index PCI, death from any cause, nonfatal myocardial infarction (defined by a new Q wave in two or more leads or a total creatine kinase level or creatine kinase MB fraction that was ≥3 times the upper limit of the normal range during hospitalization for the index PCI or that was ≥2 times the upper limit of the normal range after discharge), or urgent target-vessel revascularization during the first 30 days after the index PCI. The second was a composite of death from any cause or nonfatal myocardial infarction during the first 30 days after the index PCI, whichever occurred first. The third was a composite of death from any cause, nonfatal myocardial infarction, or urgent target-vessel revascularization during the first 30 days after the index PCI, whichever occurred first. The fourth consisted of each of the individual end points during the first 30 days after the index PCI. All events were adjudicated by an independent clinical-events committee whose members were unaware of the treatment assignments.

STATISTICAL ANALYSIS

We initially estimated that we would need to enroll 2700 patients, given a 7% incidence of any type of bleeding up to 48 hours after PCI in the unfractionated heparin group, a statistical power of 80% to detect a relative risk reduction of 47% with enoxaparin, and a type I, two-sided error rate of 2.5% for each comparison of the enoxaparin groups with the unfractionated heparin group. At a planned interim evaluation, the sample size was reevaluated, and because the overall bleeding rate was lower than the anticipated rate (3.5% vs. 4.8%), a final enrollment goal of 3690 patients was set.

All analyses were performed according to the

intention-to-treat principle and included all randomized patients analyzed according to the treatment assigned. The primary end point was also analyzed in the safety population, which included all patients who received at least one dose of study drug, analyzed according to the treatment actually received. For all end-point analyses, each enoxaparin dose was compared with unfractionated heparin. The Simes adjustment for multiplicity was applied to ensure a global type I error of 0.05: if both P values were 0.05 or less, both were considered to indicate statistical significance; if the highest P value was greater than 0.05, the other P value had to be 0.025 or less to be considered to indicate statistical significance.[27] Analyses were performed with SAS statistical software, version 8.2 (SAS Institute).

Logistic-regression analysis was used to compare the incidence of the primary end point between the enoxaparin and unfractionated heparin groups, with adjustment for the use or nonuse of glycoprotein IIb/IIIa inhibitors. If enoxaparin was not found to be superior to unfractionated heparin, we evaluated whether enoxaparin was noninferior to unfractionated heparin with the use of a two-sided, adjusted confidence interval (CI) for the differences in event rates as planned; the noninferiority margin was set at 30% of the observed bleeding rates in the unfractionated heparin group.

For secondary end points, target anti–factor Xa levels or activated clotting times were analyzed with a logistic-regression model, with adjustment for the use or nonuse of glycoprotein IIb/IIIa inhibitors. The objective for the composite quadruple end point was to test for the noninferiority of the enoxaparin doses with the use of a two-sided CI of the difference in event rates; the noninferiority margin was set at 39% of the observed rates in the unfractionated heparin group. Time-to-event analyses for the other secondary end points up to day 30 were performed with Cox proportional-hazards models.

An independent data-monitoring committee followed the progress of the trial to ensure that patient safety was not compromised. The committee met four times during the trial; the fourth interim analysis, which included 3089 patients, indicated that there were more deaths from any cause in the group given 0.5 mg of enoxaparin per kilogram (9 patients) than in either the unfractionated heparin group (3 patients, P=0.1477) or the group given 0.75 mg of enoxaparin per kilogram (1 patient, P=0.0265). On the basis of the Pocock boundary of 0.0266, the committee recommended that randomization to the group given 0.5 mg of enoxaparin per kilogram be discontinued. Enrollment was suspended in that group on November 22, 2004, just before the end of the enrollment period in December 2004. Because the decision to stop enrollment in this group could have altered decisions about the inclusion of a patient or the conduct of the study, the final analyses were adjusted for whether a patient underwent randomization before or after November 22, 2004.

Table 1. Definitions of Major and Minor Bleeding.

Major bleeding*
Fatal bleeding
Retroperitoneal, intracranial, or intraocular bleeding
Bleeding that causes hemodynamic compromise requiring specific treatment
Bleeding that requires intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event
Clinically overt bleeding, requiring any transfusion of ≥1 unit of packed red cells or whole blood
Clinically overt bleeding, causing a decrease in hemoglobin of ≥3 g/dl (or, if hemoglobin level not available, a decrease in hematocrit of ≥10%)
Minor bleeding†
Gross hematuria not associated with trauma (e.g., from instrumentation)
Epistaxis that is prolonged, repeated, or requires plugging or intervention
Gastrointestinal hemorrhage
Hemoptysis
Subconjunctival hemorrhage
Hematoma >5 cm or leading to prolonged or new hospitalization
Clinically overt bleeding, causing a decrease in hemoglobin of 2 to 3 g/dl
Uncontrolled bleeding requiring protamine sulfate administration

* Major bleeding was defined as bleeding that met at least one of the criteria listed.
† Minor bleeding was defined as bleeding that did not meet any of the criteria for major bleeding and that met at least one of the criteria for minor bleeding.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between January 2004 and December 2004, 3528 patients were enrolled: 1070 were randomly assigned to receive 0.5 mg of enoxaparin per kilo-

gram intravenously, 1228 to receive 0.75 mg of enoxaparin per kilogram intravenously, and 1230 to receive unfractionated heparin intravenously. Baseline characteristics were well balanced among the treatment groups (Table 2).

CHARACTERISTICS OF THE PROCEDURE

The procedural characteristics were similar for all three groups (Table 2). Of patients receiving unfractionated heparin, 16.5% received at least one additional bolus because of a low activated clotting time. At least one additional bolus of enoxaparin was administered during a prolonged procedure (>2 hours) in 0.6% of patients receiving 0.5 mg of enoxaparin per kilogram and 0.2% of patients receiving 0.75 mg of enoxaparin per kilogram. The median activated clotting time at the start and end of PCI was 336 and 292 seconds, respectively, for patients receiving unfractionated heparin alone and 300 and 255 seconds, respectively, for patients receiving unfractionated heparin with glycoprotein IIb/IIIa inhibitors.

PRIMARY END POINT

Non–CABG-related major or minor bleeding during the first 48 hours occurred in 5.9% of patients assigned to receive 0.5 mg of enoxaparin per kilogram, 6.5% of patients assigned to receive 0.75 mg of enoxaparin per kilogram, and 8.5% of patients assigned to receive unfractionated heparin (Table 3 and Fig. 1). These values represent a relative reduction of 31% in the primary end point with 0.5 mg of enoxaparin per kilogram as compared with unfractionated heparin, meeting the criteria for the superiority of enoxaparin over unfractionated heparin (P=0.01), and a 24% relative reduction with 0.75 mg of enoxaparin per kilogram (P=0.051), meeting the prespecified criteria for noninferiority (95% CI, −4.0 to 0.0; excluding the noninferiority margin of 30% [absolute

Table 2. Baseline Characteristics of Patients and Procedures.*

Characteristic	0.5 mg of Enoxaparin per Kilogram (N=1070)	0.75 mg of Enoxaparin per Kilogram (N=1228)	Unfractionated Heparin (N=1230)	P Value
Age — yr	63.4±10.5	63.6±10.2	63.5±10.2	0.89
Age ≥75 yr — no./total no. (%)	179/1070 (16.7)	181/1228 (14.7)	184/1230 (15.0)	0.36
Male sex — no./total no. (%)	799/1070 (74.7)	934/1228 (76.1)	910/1230 (74.0)	0.48
Weight — kg†	84.0±16.9	84.2±16.7	83.3±16.0	0.34
Creatinine clearance — no./total no. (%)				
>30 to 60 ml/min	181/1043 (17.4)	222/1202 (18.5)	217/1208 (18.0)	0.79
≤30 ml/min	14/1043 (1.3)	6/1202 (0.5)	19/1208 (1.6)	0.03
Diabetes — no./total no. (%)	324/1070 (30.3)	358/1227 (29.2)	380/1230 (30.9)	0.64
Prior myocardial infarction — no./total no. (%)				
>48 hr to 7 day	16/1070 (1.5)	25/1227 (2.0)	24/1230 (2.0)	0.61
≤48 hr	4/1070 (0.4)	9/1227 (0.7)	3/1230 (0.2)	0.18
Prior unstable angina — no./total no. (%)				
>48 hr to 7 day	72/1069 (6.7)	86/1227 (7.0)	82/1230 (6.7)	0.94
≤48 hr	55/1069 (5.1)	72/1227 (5.9)	60/1230 (4.9)	0.53
Prior PCI — no./total no. (%)	371/1070 (34.7)	448/1227 (36.5)	479/1230 (38.9)	0.10
Prior CABG — no./total no. (%)	154/1070 (14.4)	156/1227 (12.7)	186/1230 (15.1)	0.21
Platelet count <80,000/mm^3 — no./total no. (%)	1/1043 (0.1)	1/1193 (0.1)	0/1203	0.55
Hemoglobin ≤10 g/dl for women or ≤11 g/dl for men — no./total no. (%)	18/1046 (1.7)	39/1201 (3.2)	39/1209 (3.2)	0.05
Concomitant medications — no./total no. (%)				
Before PCI				
Long-term treatment with thienopyridine	510/1070 (47.7)	538/1228 (43.8)	590/1229 (48.0)	0.07
Long-term treatment with aspirin	891/1070 (83.3)	1056/1228 (86.0)	1063/1230 (86.4)	0.07

margin, +2.6%]). This effect was primarily driven by the 57% reduction in non–CABG-related major bleeding (absolute risk reduction, 1.6%) in both enoxaparin groups (0.5 mg per kilogram, 1.2%, vs. 2.8% in the unfractionated heparin group, P=0.004; 0.75 mg per kilogram, 1.2% vs. 2.8%, P=0.007) (Table 3 and Fig. 1). Among patients who did not receive glycoprotein IIb/IIIa inhibitors, non–CABG-related major or minor bleeding at 48 hours occurred in 4.1% of those in the group given 0.5 mg of enoxaparin per kilogram, 3.6% of those given 0.75 mg of enoxaparin per kilogram, and 6.8% of those given unfractionated heparin; among patients who received glycoprotein IIb/IIIa inhibitors, the rates were 8.6%, 10.8%, and 11.2%, respectively. Transfusion rates during the first 48 hours after PCI were extremely low (Table 3).

Similar results were obtained in the analysis of safety: the incidence of the primary end point was significantly reduced among patients receiving 0.5 mg of enoxaparin per kilogram, as compared with patients receiving unfractionated heparin (6.1% vs. 8.6%, P=0.02) but not among patients receiving 0.75 mg of enoxaparin per kilogram (6.7% vs. 8.6%, P=0.07). The incidence of major bleeding was significantly reduced in the group given 0.5 mg of enoxaparin per kilogram (1.3%, vs. 2.8% in the unfractionated heparin group; P=0.005) and the group given 0.75 mg of enoxaparin per kilogram (1.3% vs. 2.8%, P=0.008).

Consistent results were found across all major subgroups with respect to the primary end point. Multivariate analysis showed that significant independent correlates of the primary end point included treatment with 0.5 mg of enoxaparin per kilogram but not treatment with 0.75 mg of enoxaparin per kilogram (Fig. 2).

Although not prespecified in the protocol, bleeding that was classified according to the

Table 2. (Continued.)

Characteristic	0.5 mg of Enoxaparin per Kilogram (N=1070)	0.75 mg of Enoxaparin per Kilogram (N=1228)	Unfractionated Heparin (N=1230)	P Value
Day of PCI				
Glycoprotein IIb/IIIa inhibitor	433/1070 (40.5)	499/1228 (40.6)	491/1230 (39.9)	0.93
Thienopyridine	1007/1069 (94.2)	1158/1226 (94.5)	1170/1230 (95.1)	0.59
Aspirin	986/1068 (92.3)	1147/1224 (93.7)	1159/1228 (94.4)	0.13
Thrombolytic agent	5/1049 (0.5)	4/1215 (0.3)	4/1217 (0.3)	0.83
Coronary intervention				
PCI — no./total no. (%)	1035/1070 (96.7)	1205/1228 (98.1)	1205/1230 (98.0)	0.06
Stent procedure — no./total no. (%)	974/1035 (94.1)	1126/1205 (93.4)	1133/1205 (94.0)	0.77
Drug-eluting stent — no./total no. (%)	608/1035 (58.7)	669/1205 (55.5)	675/1205 (56.0)	0.26
Target vessel — no./total no. (%)				
Left anterior descending coronary artery	486/1035 (47.0)	564/1205 (46.8)	546/1205 (45.3)	0.68
Left circumflex coronary artery	329/1035 (31.8)	362/1205 (30.0)	375/1205 (31.1)	0.66
Right coronary artery	376/1035 (36.3)	456/1205 (37.8)	484/1205 (40.2)	0.17
Left main coronary artery	13/1035 (1.3)	17/1205 (1.4)	12/1205 (1.0)	0.65
Saphenous vein or artery graft	43/1035 (4.2)	49/1205 (4.1)	43/1205 (3.6)	0.74
Intervention in ≥2 vessels — no./total no. (%)	161/1035 (15.6)	184/1205 (15.3)	207/1205 (17.2)	0.39
Closure device used — no./total no. (%)	408/1034 (39.5)	470/1202 (39.1)	478/1205 (39.7)	0.96
Time from end of PCI to sheath removal — min‡				
Median	54	194	144	<0.001
Interquartile range	1–259	1–295	1–254	

* Plus–minus values are means ±SD. Because of rounding, percentages may not total 100.
† Data were missing for three patients in the group given 0.5 mg of enoxaparin per kilogram, two patients given 0.75 mg of enoxaparin per kilogram, and two patients given unfractionated heparin.
‡ Data were missing for 45 patients in the group given 0.5 mg of enoxaparin per kilogram, 49 patients given 0.75 mg of enoxaparin per kilogram, and 43 patients given unfractionated heparin.

Table 3. End Points.*

End Point	Unfractionated Heparin (N=1230)	0.5 mg of Enoxaparin per Kilogram (N=1070)			0.75 mg of Enoxaparin per Kilogram (N=1228)		
	No. of Patients (%)†	No. of Patients (%)†	Value	P Value	No. of Patients (%)†	Value	P Value
Non–CABG-related bleeding in the first 48 hr‡	105 (8.5)	63 (5.9)		0.01	80 (6.5)		0.051
Absolute difference — % (95% CI)			–2.6 (–4.7 to –0.6)			–2.0 (–4.0 to 0.0)	
Non–CABG-related major bleeding	34 (2.8)	13 (1.2)		0.004	15 (1.2)		0.007
Resulting in death	0	3 (0.3)		0.10	0		—
Retroperitoneal, intracranial, or intraocular	6 (0.5)	2 (0.2)		0.30	2 (0.2)		0.29
Resulting in hemodynamic compromise requiring specific treatment	11 (0.9)	3 (0.3)		0.06	5 (0.4)		0.13
Requiring intervention or decompression of closed space to stop or control the event	9 (0.7)	2 (0.2)		0.06	8 (0.7)		0.81
Clinically overt, with any transfusion of ≥1 unit of packed red cells or whole blood	14 (1.1)	4 (0.4)		0.04	9 (0.7)		0.30
Clinically overt, with a ≥3 g/dl decrease in hemoglobin	18 (1.5)	10 (0.9)		0.25	10 (0.8)		0.13
Non–CABG-related minor bleeding	72 (5.9)	51 (4.8)		0.30	65 (5.3)		0.53
TIMI bleeding§	27 (2.2)	21 (2.0)		0.70	20 (1.6)		0.31
Major	4 (0.3)	3 (0.3)		1.00	2 (0.2)		0.69
Minor	23 (1.9)	19 (1.8)		0.87	18 (1.5)		0.43
GUSTO bleeding¶	314 (25.5)	223 (20.8)		0.008	311 (25.3)		0.91
Moderate or severe	18 (1.5)	6 (0.6)		0.03	10 (0.8)		0.13
Transfusion	12 (1.0)	5 (0.5)		0.16	10 (0.8)		0.67
Composite of non–CABG-related major bleeding up to 48 hr, death from any cause, nonfatal MI, or UTVR during the first 30 days‖	101 (8.2)	74 (6.9)		0.44	94 (7.7)		0.63
Absolute difference — % (95% CI)			–0.9 (–3.1 to 1.4)			–0.5 (–2.6 to 1.6)	
Composite of death from any cause, nonfatal MI, or UTVR during the first 30 days	72 (5.8)**	66 (6.2)**		0.51	84 (6.8)**		0.30
Hazard ratio (95% CI)			1.12 (0.79 to 1.60)			1.18 (0.86 to 1.62)	
Composite of death from any cause or nonfatal MI during the first 30 days	70 (5.6)**	59 (5.6)**		0.91	79 (6.4)**		0.42
Hazard ratio (95% CI)			1.02 (0.71 to 1.47)			1.14 (0.83 to 1.58)	
Death from any cause during the first 30 days††	5 (0.4)**	10 (1.0)**		0.07	3 (0.2)**		0.50
Hazard ratio (95% CI)			3.35 (0.92 to 12.19)			0.61 (0.15 to 2.54)	
Nonfatal MI during the first 30 days	65 (5.2)**	50 (4.7)**		0.64	76 (6.1)**		0.32
Hazard ratio (95% CI)			0.91 (0.62 to 1.34)			1.18 (0.85 to 1.65)	

UTVR during the first 30 days	8 (0.7)**	8 (0.8)**		0.58	14 (1.1)**	0.20
Hazard ratio (95% CI)		1.35 (0.47 to 3.88)			1.77 (0.74 to 4.21)	
Within target anticoagulation range during the procedure‡‡	223 (19.7)	771 (78.8)		<0.001	1045 (91.8)	<0.001

* Absolute differences, P values, and hazard ratios are for the comparison with the unfractionated heparin group. Hazard ratios were based on the Cox model. MI denotes myocardial infarction, and UTVR urgent target-vessel revascularization.

† Percentages are calculated as the number divided by the total number unless otherwise noted.

‡ The noninferiority margin was 2.6%.

§ The TIMI trial criteria were as follows. Major bleeding was defined as non–CABG-related bleeding with a decrease in the hemoglobin level of ≥5 g per deciliter or an absolute decrease in the hematocrit of ≥15%, the need for the transfusion of >5 U of blood, or intracranial bleeding. Minor bleeding was defined as non–CABG-related gastrointestinal or genitourinary bleeding, non–CABG-related bleeding with a decrease in the hemoglobin level of ≥3 g per deciliter or an absolute decrease in the hematocrit of ≥10%, the need for the transfusion of >3 U of blood, any absolute decrease in the hemoglobin level of ≥4 g per deciliter or an absolute decrease in the hematocrit of ≥12%, or the need for the transfusion of >4 U of blood (not related to CABG).

¶ The GUSTO criteria were as follows. Mild bleeding was defined by non–CABG-related bleeding up to 48 hours with no need for transfusion and no hemodynamic compromise, moderate bleeding by non–CABG-related bleeding up to 48 hours with transfusion required, and severe or life-threatening bleeding by non–CABG-related bleeding up to 48 hours with hemodynamic compromise.

‖ The noninferiority margin was 3.2%.

** These values are reported as hazard rates.

†† The adjusted P value for the comparison of the group given 0.5 mg of enoxaparin per kilogram with the group given 0.75 mg per kilogram is 0.06.

‡‡ The target ranges were an anti–factor Xa level of 0.5 to 1.8 IU per milliliter for enoxaparin and an activated clotting time of 200 to 300 seconds with glycoprotein IIb/IIIa inhibitors or 300 to 350 seconds without glycoprotein IIb/IIIa inhibitors for unfractionated heparin. The analysis included 978 patients in the group given 0.5 mg of enoxaparin per kilogram, 1139 patients in the group given 0.75 mg of enoxaparin per kilogram, and 1134 in the group given unfractionated heparin.

Thrombolysis in Myocardial Infarction (TIMI) trial[28] criteria and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study criteria[29] was also assessed (Table 3). The rates of TIMI bleeding (major or minor) were not significantly different among the groups. The rate of GUSTO bleeding was significantly reduced only in the group given 0.5 mg of enoxaparin per kilogram.

SECONDARY END POINTS

Prespecified target anti–factor Xa levels of 0.5 to 1.8 IU per milliliter (the main secondary efficacy end point) were achieved in significantly more patients receiving enoxaparin (78.8% in the group given 0.5 mg per kilogram and 91.8% in the group given 0.75 mg per kilogram) than in patients receiving unfractionated heparin adjusted for the activated clotting time (19.7%, P<0.001 for both comparisons) (Table 3).

When a narrower anti–factor Xa range was selected (0.5 to 1.2 IU per milliliter), corresponding to adequate anticoagulation levels in the treatment of acute coronary syndrome,[25,26,30] 75.5% of patients given 0.5 mg of enoxaparin per kilogram reached the target range, as did 59.4% of patients given 0.75 mg of enoxaparin per kilogram. Both these proportions were significantly higher than that in the group given unfractionated heparin (P<0.001 for both comparisons).

The composite quadruple end point occurred in 6.9% of patients receiving 0.5 mg of enoxaparin per kilogram and 7.7% of those receiving 0.75 mg of enoxaparin per kilogram, as compared with 8.2% of patients receiving unfractionated heparin, meeting the prespecified criteria for noninferiority for both enoxaparin doses (Table 3). The incidence of death from any cause or nonfatal myocardial infarction during the first 30 days after PCI did not differ significantly among the three groups (Fig. 3 and Table 3). No significant difference was observed among the three groups in the incidence of the composite end point of death from any cause, nonfatal myocardial infarction, or urgent target-vessel revascularization during the first 30 days or its individual components (Table 3).

The mortality rate during an interim analysis in the group given 0.5 mg of enoxaparin per kilogram (10 patients [1.0%]), which led to early termination of enrollment in that group, was not

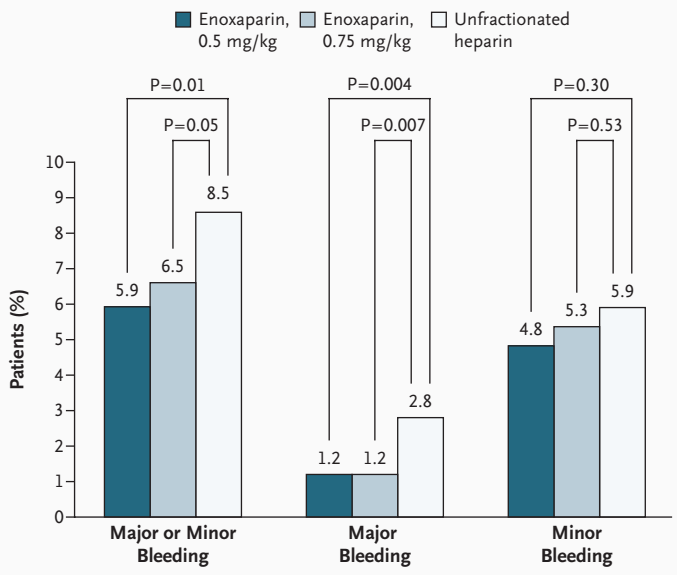

Figure 1. Incidence of Non–CABG-Related Major or Minor Bleeding during the First 48 Hours.

The 95% CIs for adjusted differences between groups for non–CABG-related major or minor bleeding during the first 48 hours were −4.7 to −0.6% for comparison of the group given 0.5 mg of enoxaparin per kilogram with the group given unfractionated heparin and −4.0% to 0.0% for the comparison of the group given 0.75 mg of enoxaparin per kilogram with the group given unfractionated heparin, with a noninferiority margin of 2.6%.

significantly higher in the final analysis than the rate in the group given unfractionated heparin (5 patients [0.4%]) or in the group given 0.75 mg of enoxaparin per kilogram (3 patients [0.2%]) (Table 3). Four deaths in the group given 0.5 mg of enoxaparin per kilogram were considered by the investigators to be possibly related to treatment. These included one cardiac arrest after successful PCI and hospital discharge (on day 4), one intracranial hemorrhage (on day 2), one episode of cardiac tamponade related to peri-procedure coronary rupture (on day 1), and one peri-procedure coronary occlusion after rotablator dissection of the main coronary trunk (on day 1). None of the deaths in the other two groups were considered to be possibly related to treatment.

DISCUSSION

We compared the safety of intravenous enoxaparin with that of unfractionated heparin in elective PCI as currently practiced (including the frequent use of drug-eluting stents and glycoprotein IIb/IIIa inhibitors as well as almost universal use of clopidogrel). A dose of 0.5 mg of enoxaparin per kilogram significantly reduced the primary end point of any bleeding (as prospectively defined by our protocol), as compared with a regimen of unfractionated heparin adjusted for activated clotting time, whereas a dose of 0.75 mg of enoxaparin per kilogram was noninferior to unfractionated heparin with respect to this end point. Both doses of enoxaparin significantly reduced the incidence of major bleeding, as compared with unfractionated heparin. The benefit of the 0.5-mg dose of enoxaparin per kilogram with respect to bleeding was also evident with the use of the GUSTO criteria but was not significant with the use of the TIMI criteria. These definitions, developed for use in trials of fibrinolysis, may not be optimal for assessing the risk of bleeding after PCI.

The effect of enoxaparin on the risk of bleeding was achieved with the use of a treatment protocol that was simpler than that typically used for unfractionated heparin. Enoxaparin was administered as a single intravenous bolus before the start of PCI, without anticoagulation monitoring; a similar dose was used whether or not glycoprotein IIb/IIIa inhibitors were given; and immediate removal of the sheath after PCI was recommended with the 0.5-mg dose of enoxaparin per kilogram.

As compared with unfractionated heparin, enoxaparin resulted in a significant increase (by a factor of four) in the rate of achievement of target anticoagulation levels. This finding highlights the superior bioavailability of enoxaparin; in contrast, unfractionated heparin requires careful coagulation monitoring. Whether there is an optimal anti–factor Xa level with enoxaparin therapy among patients undergoing PCI is still unknown, although it was shown recently that such levels were independently associated with the risk of death at 30 days in a large population of patients with non–ST-elevation acute coronary syndrome.[25] In our study, even when we aimed for a tighter anti–factor Xa range (0.5 to 1.2 IU per milliliter),[25,26,30] the results obtained with enoxaparin remained significantly more predictable and stable than those obtained with unfractionated heparin anticoagulation: more patients reached the target range with the 0.5-mg dose of enoxaparin per kilogram.

There was no significant difference in the double or triple ischemic end point or any individual component of the composite end point, in-

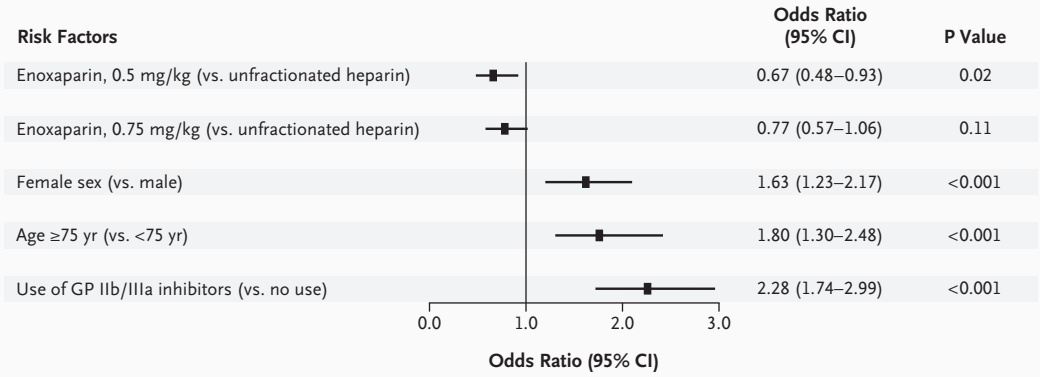

Figure 2. Odds Ratios from a Multivariate Analysis of Risk Factors for Non–CABG-Related Major or Minor Bleeding during the First 48 Hours.

The following variables were used in the multivariate analysis: age (≥75 years vs. <75 years); sex; smoking status (current smoker vs. former smoker or no history of smoking); the presence or absence of obesity, diabetes, hypertension, hypercholesterolemia, renal insufficiency (creatinine clearance, 60 ml or less per minute), peripheral arterial disease, a family history of coronary artery disease, unstable angina or myocardial infarction within the previous 7 days, a hemoglobin level at entry of ≤10 g per deciliter for women or 11 g per deciliter for men, and a platelet count at entry of ≤80,000 per mm^3; the number of diseased arteries (1 vs. 2 or ≥3); the use or nonuse of enoxaparin, another low-molecular-weight heparin, unfractionated heparin, or a direct thrombin inhibitor within the previous 7 days; the use or nonuse of warfarin or other vitamin K antagonists within the previous 7 days; sheath size (<7 French vs. ≥7 French); the use or nonuse of glycoprotein IIb/IIIa inhibitors during PCI; the use or nonuse of other antiplatelet drugs (aspirin or clopidogrel); country; time of randomization (before November 22, 2004, vs. after November 22, 2004); and treatment group. GP denotes glycoprotein.

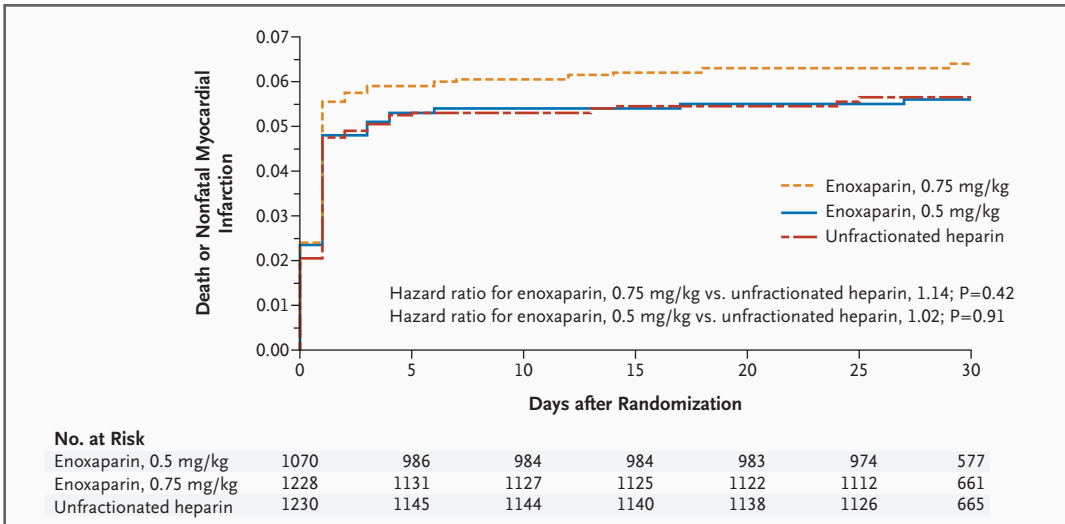

Figure 3. Kaplan–Meier Estimates of Death or Nonfatal Myocardial Infarction during the First 30 Days after PCI.

P values were based on hazard ratios from the Cox model.

cluding mortality, between patients treated with enoxaparin and those treated with unfractionated heparin. However, there were wide CIs for the ischemic end points (Table 3), and our trial was not powered to detect differences or draw conclusions with regard to these measures of drug efficacy. The mortality rate in the trial was low (0.5%) and similar to that in other recent PCI trials.[31-33] The early closure of the low-dose enoxaparin group was based on an apparent increase

in the number of deaths from any cause as compared with the number in the group given unfractionated heparin. In the final analysis, the apparent increase was found to be nonsignificant, but the CIs were wide. For the combined end point incorporating both bleeding and ischemic events, both doses of enoxaparin were noninferior to unfractionated heparin.

In summary, the STEEPLE trial demonstrated that, depending on the dose, intravenous enoxaparin is associated with bleeding rates that are similar to or lower than those with unfractionated heparin in patients undergoing elective PCI. The resulting levels of anticoagulation were more predictable with enoxaparin than with unfractionated heparin. The slightly but not significantly higher death rate with low-dose enoxaparin remains unexplained. Whether the rates of ischemic events are similar for enoxaparin and unfractionated heparin was not definitively established.

Supported by Sanofi-Aventis.

Dr. Montalescot reports having received grant support, consulting fees, and lecture fees from Sanofi-Aventis, Eli Lilly, and Bristol-Myers Squibb; consulting fees and lecture fees from Merck Sharp & Dohme; consulting fees from Procter & Gamble, AstraZeneca, and Schering-Plough; and lecture fees from GlaxoSmithKline and Nycomed. Dr. White reports having received grant support, consulting fees, and lecture fees from Sanofi-Aventis, the Medicines Company, and AstraZeneca and grant support from Procter & Gamble, Alexion, Schering-Plough, and Eli Lilly. Dr. Gallo reports having received grant support, consulting fees, and lecture fees from Sanofi-Aventis; lecture fees from Abbott, Oryx Pharmaceuticals, and Biovail Pharmaceuticals; and consulting fees from Biovail Pharmaceuticals. Dr. Cohen reports having received grant support from Aventis Pharmaceuticals, consulting fees from Sanofi-Aventis and AstraZeneca, and lecture fees from Sanofi-Aventis, Merck, and Schering. Dr. Steg reports having received grant support from Sanofi-Aventis and Bristol-Myers Squibb; consulting fees from Sanofi-Aventis, Takeda, AstraZeneca, Merck Sharp & Dohme, GlaxoSmithKline, Bristol-Myers Squibb, and Servier; and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, Merck Sharp & Dohme, Nycomed, GlaxoSmithKline, Boehringer Ingelheim, and Servier. Dr. Aylward reports having received grant support from Sanofi-Aventis, Procter & Gamble, Alexion, the Medicines Company, Schering-Plough, and Eli Lilly and consulting and lecture fees from Sanofi-Aventis and Bristol-Myers Squibb. Dr. Bode reports having received consulting fees and lecture fees from Sanofi-Aventis, Eli Lilly, and GlaxoSmithKline; consulting fees from Nycomed; and lecture fees from AstraZeneca. Dr. Chiariello reports having received consulting fees from Schering-Plough and Nycomed and lecture fees from Merck Sharp & Dohme, GlaxoSmithKline, and IFB Stroder. Dr. King reports having received grant support from Medtronic and lecture fees from Sanofi-Aventis and Bristol-Myers Squibb. Dr. Harrington reports having received grant support, consulting fees, and lecture fees from Sanofi-Aventis. Dr. Steinhubl reports having received consulting fees from Sanofi-Aventis, the Medicines Company, Eli Lilly, and AstraZeneca. No other potential conflict of interest relevant to this article was reported.

We are indebted to the patients who agreed to participate in this trial; to the study contributors; to Dr. Marcel Meijer, who assisted in the preparation of this manuscript; and to the investigators who recruited patients.

APPENDIX

The following investigators participated in the STEEPLE trial: **Steering Committee** — *France* — G. Montalescot (Cochair), P.G. Steg; *Australia* — P.E.G. Aylward; *New Zealand* — H.D. White; *Belgium* — W. Desmet; *Canada* — R. Gallo; *Germany* — C. Bode; *Italy* — M. Chiariello; *Spain* — C. Macaya; *United States* — S.R. Steinhubl (Cochair), R.A. Harrington, S.B. King III, M. Cohen; **Data-Monitoring Committee** — *United States* — M. Klapholz (Chair), D. Mukherjee; *United Kingdom* — N. Stallard; *Belgium* — W. Wijns; **Clinical Events Committee** — *United States* — B.R. Chaitman (Chair), P. Bjerrgaard, R. Bach; **Publication Committee** — *France* — G. Montalescot (Chair); *United States* — S.R. Steinhubl; *New Zealand* — H.D. White; *Canada* — R. Gallo; **Key Sanofi-Aventis Personnel** — V. Bertuit, W.B. Drusedum (study managers), D. Sbaï (study coordinator), G. Salette (statistician), A. Wajman, W. Byra, M.-F. Bregeault (clinical directors); **Investigators** — *Australia* — D. Chew, L. Arnolda, I. Meredith, C. Jurgens, A. Farshid; *Belgium* — W. Desmet, P. Coussement, P. Vermeersch, K. Dujardin, M. Vrolix; *Canada* — J. Ducas, A. Fung, R. Gallo, W. Hui, W. Kostuk, R. Kuritzky, C. Lazzam, A.-U.-R. Quraishi, B. Rose, J. Ross, E. Schampaert, F. Spence, J. Velianou, J. Webb, R. Welsh; *France* — G. Montalescot, O. Wittenberg, H. Le Breton, J.-M. LaBlanche, H. Eltchaninoff, P. Coste, P.G. Steg, F. Paganelli, B. Charbonnier, D. Carrie, N. Meneveau, T. Lefevre, G. Bayet; *Germany* — C. Bode, M. Beyer, K.H. Kuck, T. Heitzer, F.M. Bahr, L. Pizzukki, G. Richardt, R. Tolg, H. Darius, S. Behrens, W. Jung, T. Munzel; *Italy* — M. Chiariello, P. Golino, A. Bartorelli, G. Ambrosio, A.S. Petronio, C. Tamburino, P. Danna, G. Richichi; *New Zealand* — H.D. White, S. Pasupati; *Spain* — C. Macaya, R. Melgares, J.M. Ruiz Nodar, J. Moreu, J. Hernandez Garcia, F. Fernandez-Vazquez, C. Moris, A. Cequier, T. Colman, M. Sanmartin, I. Lekuona, A. Rincon de Arellano; *United States* — A. Arnold, M. D'Urso, N. Perlmutter, M. Turco, J. Smith, S. Jain, P. Kraft, N. Lakkis, G. Levine, S. Yakubov, H. Ladley, E. Rivera, M. Cohen, E. Goudreau, J. Moss, M. Fenster, E. Fry, M. Lawrence, G. Schaer, T. Stuckey, M. Moran, V.K. Raman, A. Moreyra, M. Warner, B. Bartolet, A.R.Z. Masud, R. Carlson, F. Tilli, D. Henderson, D. Churchill, R. Piana, N. Shadoff, P. Counihan, S. Brener, A. Sonel, M. Zughaib, R.A. Harrington, N. Srivastava, B. Murad, D. Lee, M. DeGregorio, B. Jaski, R. Agah, J. Breall, L. Iliadis, P. Fenner, W. French, M. Lim, N. Mayer, J. Martin, T. Shapiro, D. Moliterno, T. Jayasundera, C. Nelson, G.L. Chang, F. Ling, G. Levine, D. Marks, M. Ayres.

REFERENCES

1. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines) — executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 2001;37:2215-39.
2. Silber S, Albertsson P, Aviles FF. Guidelines for percutaneous coronary interventions: the Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J 2005; 26:804-47.
3. Cohen M. The role of low-molecular-weight heparin in the management of acute coronary syndromes. J Am Coll Cardiol 2003;41:Suppl 4:55S-61S.
4. Collet JP, Montalescot G, Lison L, et

al. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. Circulation 2001;103:658-63.
5. Ferguson JJ, Antman EM, Bates ER, et al. Combining enoxaparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes: final results of the National Investigators Collaborating on Enoxaparin-3 (NICE-3) study. Am Heart J 2003;146:628-34.
6. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004;292:45-54.
7. Choussat R, Montalescot G, Collet JP, et al. A unique, low dose of intravenous enoxaparin in elective percutaneous coronary intervention. J Am Coll Cardiol 2002; 40:1943-50.
8. Borentain M, Montalescot G, Bouzamondo A, Choussat R, Hulot JS, Lechat P. Low-molecular-weight heparin vs. unfractionated heparin in percutaneous coronary intervention: a combined analysis. Catheter Cardiovasc Interv 2005;65:212-21.
9. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. Semin Thromb Hemost 2000;26:Suppl 1:31-8.
10. Montalescot G, Philippe F, Ankri A, et al. Early increase of von Willebrand factor predicts adverse outcome in unstable coronary artery disease: beneficial effects of enoxaparin. Circulation 1998;98:294-9.
11. Montalescot G, Collet JP, Lison L, et al. Effects of various anticoagulant treatments on von Willebrand factor release in unstable angina. J Am Coll Cardiol 2000; 36:110-4.
12. Montalescot G, Bal-dit-Sollier C, Chibedi D, et al. Comparison of effects on markers of blood cell activation of enoxaparin, dalteparin, and unfractionated heparin in patients with unstable angina pectoris or non-ST-segment elevation acute myocardial infarction (the ARMADA study). Am J Cardiol 2003;91:925-30.
13. Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. Circulation 1998;97:251-6.
14. Kereiakes DJ, Grines CL, Fry E, et al. Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. J Invasive Cardiol 2001; 13:272-8.
15. Chen WH, Lau CP, Lau YK, et al. Stable and optimal anticoagulation is achieved with a single dose of intravenous enoxaparin in patients undergoing percutaneous coronary intervention. J Invasive Cardiol 2002;14:439-42.
16. Rabah MM, Premmereur J, Graham M, et al. Usefulness of intravenous enoxaparin for percutaneous coronary intervention in stable angina pectoris. Am J Cardiol 1999;84:1391-5.
17. Drozd J, Opalińska E, Wójcik J, Madejczyk A. The use of enoxaparin during percutaneous coronary angioplasty in patients with stable angina. Kardiol Pol 2001;55: 520-4.
18. Dudek D, Dabrowski M, Ochala A, et al. Multicenter, prospective, double-blind randomized comparison of enoxaparin versus unfractionated heparin for percutaneous coronary interventions. Am J Cardiol 2000;86:Suppl 8A:15i. abstract.
19. Bhatt DL, Lee BI, Casterella PJ, et al. Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. J Am Coll Cardiol 2003;41:20-5.
20. Galeote G, Hussein M, Sobrino N, et al. Combination abciximab and enoxaparin or unfractionated heparin during percutaneous coronary intervention: a randomised study. Eur Heart J 2001;22:Suppl: 663. abstract.
21. Madan M, Radhakrishnan S, Reis M, et al. Comparison of enoxaparin versus heparin during elective percutaneous coronary intervention performed with either eptifibatide or tirofiban (the ACTION Trial). Am J Cardiol 2005;95:1295-301.
22. Miller L, Gupta A, Bertolet BD. Use of clopidogrel loading, enoxaparin, and double-bolus eptifibatide in the setting of early percutaneous coronary intervention for acute coronary syndromes. J Invasive Cardiol 2002;14:247-50.
23. Sanchez-Pena P, Hulot JS, Urien S, et al. Anti-factor Xa kinetics after intravenous enoxaparin in patients undergoing percutaneous coronary intervention: a population model analysis. Br J Clin Pharmacol 2005;60:364-73.
24. Popma JJ, Berger P, Ohman EM, Harrington RA, Grines C, Weitz JI. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:Suppl 3: 567S-599S.
25. Montalescot G, Collet JP, Tanguy ML, et al. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. Circulation 2004;110:392-8.
26. The Thrombolysis in Myocardial Infarction (TIMI) 11A Trial Investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. J Am Coll Cardiol 1997;29:1474-82.
27. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika 1986;73:751-4.
28. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. Circulation 1987;76:142-54.
29. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329: 673-82.
30. Bijsterveld NR, Moons AH, Meijers JC, Levi M, Buller HR, Peters RJ. The impact on coagulation of an intravenous loading dose in addition to a subcutaneous regimen of low-molecular-weight heparin in the initial treatment of acute coronary syndromes. J Am Coll Cardiol 2003;42:424-7.
31. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853-63. [Erratum, JAMA 2003;289:1638.]
32. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353:663-70.
33. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.

POWERPOINT SLIDES OF *JOURNAL* FIGURES AND TABLES

At the *Journal*'s Web site, subscribers can automatically create PowerPoint slides. In a figure or table in the full-text version of any article at **www.nejm.org**, click on Get PowerPoint Slide. A PowerPoint slide containing the image, with its title and reference citation, can then be downloaded and saved.