A COMPARISON OF LOW-MOLECULAR-WEIGHT HEPARIN WITH UNFRACTIONATED HEPARIN FOR UNSTABLE CORONARY ARTERY DISEASE

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ABSTRACT

Background Antithrombotic therapy with heparin plus aspirin reduces the rate of ischemic events in patients with unstable coronary artery disease. Low-molecular-weight heparin has a more predictable anticoagulant effect than standard unfractionated heparin, is easier to administer, and does not require monitoring.

Methods In a double-blind, placebo-controlled study, we randomly assigned 3171 patients with angina at rest or non–Q-wave myocardial infarction to receive either 1 mg of enoxaparin (low-molecular-weight heparin) per kilogram of body weight, administered subcutaneously twice daily, or continuous intravenous unfractionated heparin. Therapy was continued for a minimum of 48 hours to a maximum of 8 days, and we collected data on important coronary end points over a period of 30 days.

Results At 14 days the risk of death, myocardial infarction, or recurrent angina was significantly lower in the patients assigned to enoxaparin than in those assigned to unfractionated heparin (16.6 percent vs. 19.8 percent, $P = 0.019$). At 30 days, the risk of this composite end point remained significantly lower in the enoxaparin group (19.8 percent vs. 23.3 percent, $P = 0.016$). The need for revascularization procedures at 30 days was also significantly less frequent in the patients assigned to enoxaparin (27.0 percent vs. 32.2 percent, $P = 0.001$). The 30-day incidence of major bleeding complications was 6.5 percent in the enoxaparin group and 7.0 percent in the unfractionated-heparin group, but the incidence of bleeding overall was significantly higher in the enoxaparin group (18.4 percent vs. 14.2 percent, $P = 0.001$), primarily because of ecchymoses at injection sites.

Conclusions Antithrombotic therapy with enoxaparin plus aspirin was more effective than unfractionated heparin plus aspirin in reducing the incidence of ischemic events in patients with unstable angina or non–Q-wave myocardial infarction in the early phase. This benefit of enoxaparin was achieved with an increase in minor but not in major bleeding. (N Engl J Med 1997;337:447-52.)

ANTITHROMBOTIC therapy consisting of the intravenous infusion of unfractionated heparin plus oral aspirin represents the current standard of care for patients hospitalized with unstable angina or non–Q-wave myocardial infarction.[1-6] However, this treatment has a substantial failure rate, probably because of the unpredictable anticoagulant response to standard unfractionated heparin,[7] as well as its neutralization by protein binding and activated platelets,[8,9] and rebound clinical events that follow the discontinuation of unfractionated heparin.[10] The low-molecular-weight heparins have several potential advantages over unfractionated heparin. They have a more predictable anticoagulant effect with a higher ratio of anti–factor Xa to anti–factor IIa,[11] require no monitoring of anticoagulation, are resistant to inhibition by activated platelets,[8,9] and lower the incidence of heparin-induced thrombocytopenia.[12] Because of the success of low-molecular-weight heparins in previous clinical trials,[5,13,14] we undertook a double-blind, randomized comparison of the efficacy and safety of subcutaneous enoxaparin (low-molecular-weight heparin) with those of intravenous unfractionated heparin in patients with non–Q-wave coronary events (unstable angina or non–Q-wave myocardial infarction) — the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trial.

METHODS

Patient Populations

Enrollment of patients began in October 1994 and was completed in May 1996 at 176 centers in the United States, Canada,

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*Other members of the study group are listed in the Appendix.

South America, and Europe. Eligible patients were men or nonpregnant women at least 18 years of age with recent onset of angina at rest lasting at least 10 minutes and occurring within 24 hours before randomization. In addition, patients were required to have evidence of underlying ischemic heart disease as manifested by one of three criteria: (1) a new ST-segment depression of at least 0.1 mV, a transient ST-segment elevation, or T-wave changes in at least two contiguous leads; (2) a documented previous myocardial infarction or revascularization procedure; or (3) results of noninvasive or invasive testing suggesting ischemic heart disease. Exclusion criteria included the presence of a left bundle-branch block or pacemaker, persistent ST-segment elevation, angina with an established precipitating cause (e.g., heart failure or tachydysrhythmia), contraindications to anticoagulation, or a creatinine clearance rate of less than 30 ml per minute. Written informed consent was obtained from all patients. The study was approved by the institutional review board of each participating hospital.

Study Design and Treatment Protocol

The ESSENCE study was a prospective, randomized, double-blind, parallel-group, multicenter trial. Patients received either 1 mg of enoxaparin (supplied by Rhône-Poulenc Rorer, Collegeville, Pa.) per kilogram of body weight (100 anti–factor Xa units per kilogram) subcutaneously every 12 hours and an intravenous placebo bolus and infusion, or subcutaneous placebo injections and unfractionated heparin as an intravenous bolus (usually 5000 units) followed by a continuous infusion at a dose adjusted according to the activated partial-thromboplastin time. The activated partial-thromboplastin time was measured at base line and four to six hours after initiation of the study drug. The results were reported only to an independent and unblinded health care professional who acted on them according to a preapproved institutional heparin-dosing nomogram. "Dummy" heparin adjustments were ordered for patients assigned to receive intravenous placebo. The hospital nomograms typically targeted the activated partial-thromboplastin time at 55 to 85 seconds. All the patients received 100 to 325 mg of oral aspirin daily, depending on the physician's preference. The trial therapy was administered for a minimum of 48 hours and up to a maximum of 8 days. It was discontinued at the time of discharge from the hospital, a new myocardial infarction, a revascularization procedure, or death.

End Points

The primary outcome of the trial was the composite triple end point of death, myocardial infarction (or reinfarction), or recurrent angina at 14 days of follow-up. Secondary aims were to assess the triple composite end point at 48 hours and at 30 days and the double composite end point (death or myocardial infarction) at 48 hours, 14 days, and 30 days. Lastly, the incidence of major and minor hemorrhage was tabulated. All the end points were verified independently by an end-point committee whose members were unaware of treatment assignments.

Definitions

Recurrent angina was defined as one of the following: angina at rest lasting at least five minutes that was associated with a new ST-segment shift (elevation or depression) of more than 0.1 mV, or with T-wave inversions, in two contiguous electrocardiographic leads; angina without electrocardiographic changes that prompted a decision to perform a revascularization procedure; or angina after hospital discharge that resulted in rehospitalization.

Myocardial infarction was defined as (1) a total creatine kinase concentration more than twice the upper limit of normal and an above-normal concentration of creatine kinase MB (at least 3 percent of total creatine kinase), or (2) in the absence of creatine kinase or creatine kinase MB measurements, new Q waves of more than 0.04 second in at least two leads. Perioperative myocardial infarction was defined as an elevation of total creatine kinase to five times the upper limit of normal, or new Q waves of more than 0.04 second in at least two leads. A diagnosis of infarction after a percutaneous coronary intervention was made if the total creatine kinase concentration increased to three times the upper limit of normal and at least 50 percent above the previous nadir value.

Death was defined as any death, regardless of cause. Cardiac arrest from which the patient was resuscitated was also classified as a death for purposes of the end-point analysis.

Major hemorrhage was defined as bleeding resulting in death, transfusion of at least two units of blood, a fall in hemoglobin of 30 g per liter or more, or a retroperitoneal, intracranial, or intraocular hemorrhage. Minor hemorrhage was any clinically important bleeding that did not qualify as major — for example, epistaxis, ecchymosis or hematoma, or macroscopic hematuria.

Statistical Analysis

The primary analysis included all the randomized patients according to the intention-to-treat principle. A logistic-regression model was used to compare the two treatment groups, with adjustment for differences in country, with respect to the primary end point and dichotomous secondary end points. The P value indicating statistical significance for the primary end point was set at 0.048, which represents an adjustment for the preplanned interim safety analysis. Comparisons of time to an event were made by the Kaplan–Meier estimation technique. In measuring the time to an event for cases in which a patient had multiple end points, only the first event was taken into account.

RESULTS

A total of 3171 patients were enrolled in 176 hospitals in 10 countries: 1259 in Canada, 936 in the United States, 710 in Europe, and 266 in South America. The base-line characteristics of the patients according to treatment assignment are shown in Table 1. There was no significant difference in any base-line variable between the two treatment groups. At least one dose of the study drug was administered to 98 percent of the enrolled patients; however, treatment was prematurely discontinued within 48 hours for 367 patients (11.6 percent) — 207 (13.2 percent) assigned to unfractionated heparin and 160 (10.0 percent) assigned to enoxaparin. The reasons for stopping were as follows: the occurrence of an end point, 77 of 367 patients (21.2 percent); hospital discharge, 70 of 367 (19.3 percent); the need for a procedure, 66 of 367 (18.2 percent); withdrawal of consent or the physician's preference, 28 of 367 (7.7 percent); deviation from the protocol, 27 of 367 (7.4 percent); an adverse clinical event, 40 of 367 (11.0 percent); and miscellaneous or unknown reasons, 59 of 367 (16.1 percent). The assigned therapy was initiated within 12 hours of randomization in 96 percent of the patients. The median duration of treatment for both trial therapies was 2.6 days.

The ability of unfractionated heparin to maintain the activated partial-thromboplastin time in the therapeutic range (55 to 85 seconds) is shown in Table 2. Within 12 to 24 hours, 46 percent of patients treated with unfractionated heparin had an activated partial-thromboplastin time of 55 to 85 seconds. In the patients for whom information about base-line and end-of-treatment vital signs was available (3111 of 3171), the relevant antianginal medications given

during trial therapy resulted in the following decreases in blood pressure and heart rate in the unfractionated-heparin group as compared with the enoxaparin group: systolic blood pressure dropped by a mean of 15.6 mm Hg as compared with 14.0 mm Hg, diastolic blood pressure dropped by a mean of 8.2 mm Hg as compared with 7.1 mm Hg, and heart rate dropped by a mean of 5.6 beats per minute as compared with 5.1 beats per minute.

The incidence of the composite triple end point — death, myocardial infarction, or recurrent angina — at 14 days (the primary end point) and at 30 days is given in Table 3, along with each individual component of the triple end point. After 14 days of therapy, the risk of death, myocardial infarction, or recurrent angina was significantly lower among the patients assigned to enoxaparin than among those assigned to unfractionated heparin (16.6 percent vs. 19.8 percent; odds ratio, 0.80; 95 percent confidence interval, 0.67 to 0.96; P = 0.019). At 30 days the risk of death, myocardial infarction, or recurrent angina remained significantly lower in the enoxaparin group than in the unfractionated-heparin group (19.8 percent vs. 23.3 percent; odds ratio, 0.81; 95 percent confidence interval, 0.68 to 0.96; P = 0.016). The country-adjusted odds ratios did not differ significantly from the unadjusted odds ratios at the various time points (0.83 vs. 0.83 at 48 hours, 0.80 vs. 0.81 at 14 days, and 0.81 vs. 0.81 at 30 days).

Among the patients who received at least one dose of study medication, enoxaparin was also more effective: at 48 hours, the risk of the composite end point was 6.1 percent for the enoxaparin group as compared with 7.3 percent for the unfractionated-heparin group (P = 0.120), at day 14 it was 16.5 percent as compared with 19.8 percent (P = 0.017), and at day 30 it was 19.8 percent as compared with 23.4 percent (P = 0.014). Figure 1 shows the Kaplan–Meier estimates of the time to the first event (death, myocardial infarction, or recurrent angina) in the first 30 days after randomization.

The secondary composite end point of death or myocardial infarction was reached at 14 days in 4.9 percent of the enoxaparin group as compared with 6.1 percent of the unfractionated-heparin group (risk reduction, 19.9 percent; P = 0.13) and at 30 days in 6.2 percent of the enoxaparin group as compared with 7.7 percent of the unfractionated-heparin group (risk reduction, 20.4 percent; P = 0.08). Thirty days after randomization, the need for coronary revascularization was significantly less frequent among the patients assigned to enoxaparin (27.0 percent) than among those assigned to unfractionated heparin (32.2 percent, P = 0.001) (Table 4). Enoxaparin was significantly more effective than unfractionated heparin in several subgroups — patients older than 65 and those with previous long-term aspirin use, previous percutaneous transluminal coronary angioplasty, any echocardiographic changes at base line, or ST-segment depression at base line.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.

CHARACTERISTIC	TREATMENT GROUP	
	UNFRACTIONATED HEPARIN (N = 1564)	ENOXAPARIN (N = 1607)
	mean (median)	
Age (yr)	64 (65)	63 (64)
Weight (kg)	79 (77)	79 (78)
	number (percent)	
Male sex	1033 (66.1)	1079 (67.1)
Risk factors		
Family history	651 (41.6)	677 (42.1)
Current smoker	369 (23.6)	399 (24.8)
Hypertension	853 (54.5)	857 (53.3)
Hypercholesterolemia	692 (44.2)	720 (44.8)
Diabetes mellitus	339 (21.7)	360 (22.4)
Prior cardiac history*		
Positive cardiac catheterization†	676 (43.2)	702 (43.7)
Positive exercise-tolerance test	426 (27.3)	402 (25.0)
Myocardial infarction	745 (47.6)	723 (45.0)
CABG	303 (19.4)	317 (19.7)
PTCA	332 (21.2)	346 (21.5)
Electrocardiographic changes‡	894 (57.2)	897 (55.8)
ST-segment elevation	113 (7.2)	114 (7.1)
ST-segment depression	388 (24.8)	358 (22.3)
T-wave inversions	601 (38.4)	623 (38.8)

*CABG denotes coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†"Positive cardiac catheterization" indicates that coronary stenosis of at least 50 percent was revealed.

‡Electrocardiographic subcategories are not mutually exclusive.

TABLE 2. ACTIVATED PARTIAL-THROMBOPLASTIN TIMES IN PATIENTS RECEIVING UNFRACTIONATED HEPARIN.

TIME INTERVAL (HR)	ACTIVATED PARTIAL-THROMBOPLASTIN TIME		
	<55 SEC	55–85 SEC	>85 SEC
	number (percent)		
6 to <12	163 (17.4)	283 (30.3)	488 (52.2)
12 to <24	200 (15.4)	597 (46.0)	500 (38.6)
24 to <48	203 (14.8)	705 (51.3)	464 (33.8)
48 to <72	162 (18.0)	528 (58.8)	206 (22.9)
72 to <96	68 (14.9)	272 (59.6)	115 (25.2)

The serious bleeding complications are shown in Table 5. There was no significant difference between the two treatment groups with regard to serious hemorrhagic complications. The majority of such complications occurred during or after coronary bypass surgery performed after the discontinuation of

TABLE 3. INCIDENCE OF THE COMPOSITE TRIPLE END POINT AND OF COMPONENT EVENTS.*

TIME POINT	END POINT	TREATMENT GROUP		RISK REDUCTION	ODDS RATIO (95% CONFIDENCE INTERVAL)	P VALUE
		UNFRACTIONATED HEPARIN (N=1564)	ENOXAPARIN (N=1607)			
		number (percent)		percent		
48 hours	Composite triple	115 (7.4)	99 (6.2)	16.2	0.83 (0.62–1.09)	0.18
	Death	7 (0.4)	8 (0.5)	−11.2	1.12 (0.40–3.23)	0.83
	Myocardial infarction	14 (0.9)	11 (0.7)	23.5	0.76 (0.34–1.69)	0.50
	Recurrent angina	99 (6.3)	83 (5.2)	18.4	0.80 (0.60–1.09)	
	Most severe event					
	Death	7 (0.4)	8 (0.5)			
	Myocardial infarction	14 (0.9)	10 (0.6)			
	Recurrent angina	94 (6.0)	81 (5.1)			
14 days	Composite triple	309 (19.8)	266 (16.6)	16.2	0.80 (0.67–0.96)	0.02
	Death	36 (2.3)	36 (2.2)	2.7	0.98 (0.61–1.56)	0.92
	Myocardial infarction	70 (4.5)	51 (3.2)	29.1	0.70 (0.48–1.01)	0.06
	Recurrent angina	243 (15.5)	207 (12.9)	17.1	0.80 (0.65–0.98)	0.03
	Most severe event					
	Death	36 (2.3)	36 (2.2)			
	Myocardial infarction	60 (3.8)	43 (2.7)			
	Recurrent angina	213 (13.6)	187 (11.6)			
30 days	Composite triple	364 (23.3)	318 (19.8)	15.0	0.81 (0.68–0.96)	0.02
	Death	57 (3.6)	47 (2.9)	19.8	0.79 (0.53–1.18)	0.25
	Myocardial infarction	81 (5.2)	62 (3.9)	25.5	0.74 (0.52–1.03)	0.08
	Recurrent angina	281 (18.0)	252 (15.7)	12.7	0.85 (0.70–1.02)	0.08
	Most severe event					
	Death	57 (3.6)	47 (2.9)			
	Myocardial infarction	64 (4.1)	52 (3.2)			
	Recurrent angina	243 (15.5)	219 (13.6)			

*A patient may have had more than one component event in a given period.

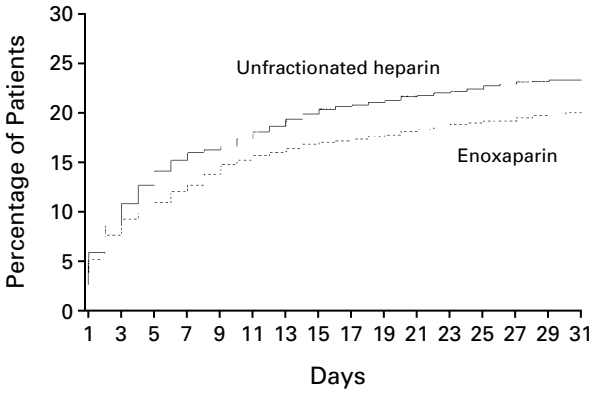

Figure 1. Kaplan–Meier Plots of the Time to a First Event over a Period of 30 Days for the Composite End Point of Death, Myocardial Infarction, or Recurrent Angina.

study medication. There was, however, a higher incidence of hemorrhagic complications overall among patients treated with enoxaparin than among those treated with unfractionated heparin: 9.4 percent versus 4.4 percent while patients were receiving the study medication and 18.4 percent versus 14.2 percent 30 days after randomization ($P=0.001$). This difference between the two groups was due to an increase in minor hemorrhagic events, with the most frequent such event being injection-site ecchymosis. There were no verified cases of heparin-induced thrombocytopenia in either treatment group, a fact that could be related in part to the short duration of study therapy (median duration, 2.6 days).

DISCUSSION

Several randomized clinical trials have demonstrated that low-molecular-weight heparins are at least as good as, if not better than, unfractionated heparin in preventing perioperative deep venous thrombosis and thromboembolism after major abdominal surgery and total hip or knee arthroplasty.[13,15-20] The benefit of low-molecular-weight heparin was not negated by an increase in hemorrhagic complications. At least two studies[21,22] have also documented the superior efficacy and safety of low-molecular-weight heparin administered at home, as compared with in-hospital intravenous unfractionated heparin, in treating patients with established deep-vein thrombosis. Recently, clinical trials have been published indicating that low-molecular-weight heparin may be beneficial in treating arterial diseases. For example, Edmondson et al.[23] observed better patency of peripheral arterial bypass grafts with subcutaneous low-molecular-weight heparin (dalteparin

[Fragmin]) than with standard aspirin plus dipyridamole. In patients with acute ischemic stroke, Kay et al.[24] compared low-molecular-weight heparin (nadroparin [Fraxiparine]) with placebo and found a significant, favorable dose-dependent effect of low-molecular-weight heparin given twice daily for 10 days with respect to death or dependency (the need for help with activities of daily living) at 6 months. There was no significant increase in the rate of hemorrhagic transformation of the infarct.

The FRISC (Fragmin during Instability in Coronary Artery Disease) study[5] evaluated combination antithrombotic therapy with aspirin and 120 IU of dalteparin (Fragmin) per kilogram given subcutaneously twice daily for up to 6 days, followed by 7500 IU daily for up to 50 days, as compared with aspirin alone in patients with acute coronary syndromes and no persistent ST-segment elevation. A significant relative-risk reduction of 48 percent in the composite end point of death or myocardial infarction was seen in the first six days of treatment. Neri Serneri et al.[25] compared subcutaneous unfractionated heparin (calciparine) with intravenous unfractionated heparin in a short-term study and observed equivalent beneficial effects in terms of the number and duration of ischemic events documented by continuous electrocardiographic recording in comparison with aspirin alone. Gurfinkel et al.,[14] however, were the first to compare low-molecular-weight heparin (nadroparin) and aspirin directly with standard intravenous unfractionated heparin and aspirin (the dose of heparin was adjusted for the activated partial-thromboplastin time) and with aspirin alone. There was a decrease of more than 50 percent in the rate of recurrent angina (44 percent vs. 21 percent) as well as a significant decrease in the rates of silent ischemia, revascularization, and minor bleeding in the group receiving low-molecular-weight heparin as compared with the groups receiving heparin plus aspirin and aspirin alone. The FRIC study,[26] a randomized but open-label (in the hospital phase) study involving 1500 patients with acute non–Q-wave coronary syndromes, compared low-molecular-weight heparin (dalteparin) and aspirin with standard intravenous adjusted-dose heparin and aspirin. In that study there was no difference in efficacy or in the incidence of hemorrhage between the patients treated with low-molecular-weight heparin and those treated with unfractionated heparin during the hospital phase.

In the ESSENCE study, in contrast, we observed a significant reduction in the number of events at 14 days that was sustained through 30 days. One difference between the ESSENCE and FRIC studies was that enoxaparin was used in ESSENCE and dalteparin was used in FRIC. Enoxaparin has a ratio of anti–factor Xa to anti–factor IIa activity of 3:1, as compared with 2:1 for dalteparin. Patients in the Thrombolysis in Myocardial Infarction 11A study,[27] who received 1 mg of enoxaparin per kilogram twice daily, had a median trough level of anti–factor Xa activity of 0.5 IU per milliliter 12 hours after the third subcutaneous injection. In contrast to the FRISC study, the duration of study therapy in the ESSENCE study was slightly more variable, making it difficult to detect a possible "rebound" after heparin withdrawal.

The significant difference between treatment groups in the ESSENCE study was driven by the differences in the rates of recurrent angina, though there was a notable reduction in the risks of both death (19.8 percent) and myocardial infarction (25.5 percent) at 30 days. The reduction in the risk of death or myocardial infarction did not reach statistical significance, however. Relative to the reductions in the risk of death and myocardial infarction seen in the FRISC study, the reductions in the risk of these end points in the ESSENCE study were smaller. This difference is probably related to our comparison of low-molecular-weight heparin plus aspirin with heparin plus aspirin (i.e., the comparison of one anticoagulant treat-

TABLE 4. COMPARISON OF REVASCULARIZATION RATES.

TYPE OF REVASCULARIZATION	TREATMENT GROUP		RISK REDUCTION	P VALUE
	UNFRACTIONATED HEPARIN (N=1564)	ENOXAPARIN (N=1607)		
	number (percent)		percent	
All revascularizations	504 (32.2)*	434 (27.0)	16.0	0.001
Coronary-artery bypass grafting	214 (13.7)	198 (12.3)	7.5	0.25
Percutaneous revascularization	293 (18.7)	236 (14.7)	19.5	0.002

*Some patients underwent both percutaneous revascularization and bypass grafting.

TABLE 5. HEMORRHAGIC AND SERIOUS ADVERSE EVENTS AT DAY 30.*

ADVERSE EVENT	TREATMENT GROUP		P VALUE
	UNFRACTIONATED HEPARIN	ENOXAPARIN	
	number (percent)		
Hemorrhage			
Major	107 (7.0)	102 (6.5)	0.57
Minor	110 (7.2)	188 (11.9)	<0.001
Stroke	7 (0.5)	7 (0.4)	
Hemorrhagic	1 (0.1)	0	
Nonhemorrhagic	6 (0.4)	7 (0.4)	
Transient ischemic attack	8 (0.5)	1 (0.1)	
Drop in platelet count of >50% from base line	56 (3.7)	39 (2.5)	0.08

*All patients who received at least one dose of study medication are included.

ment with another), in contrast to FRISC, which compared low-molecular-weight heparin with placebo (i.e., aspirin alone).

Several recent studies have compared newer antithrombotic agents, such as direct antithrombins[28] and platelet glycoprotein IIb/IIIa–receptor antagonists,[29] with standard unfractionated heparin plus aspirin in patients with acute coronary syndromes who did not have ST-segment elevations. The present study shows a significant benefit of enoxaparin over standard unfractionated heparin that is sustained for as long as 30 days in a similar patient population.

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APPENDIX

In addition to the authors, the following investigators and institutions participated in the ESSENCE study: End-Point Committee: L. Dreifus, J. Kostis, M. Freedman, J. Rand. Data and Safety Monitoring Committee: R. Makuch, J. Cairns, R. Gorlin, J. Hirsh. Statistical Analysis: *Duke Clinical Research Institute* — K. Lee, B. Weatherley, S. Stinnett, D. Beasley, C. MacAulay, R. Sparapani; *Rhône-Poulenc Rorer* — E. Genevois, J. Stephens, G. Warsi. Data Coordination: *Rhône-Poulenc Rorer* — F. Gosset, S. Long, S. Slatylak, M. Todd, J. Wiedmeyer; *Covance (Corning Besselaar)* — L. Dampman, M. Horner, I. Houlihan, D. Szemborski; *Coromed* — M. Puccio.

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