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ARTICLES

Comparison of Low-Molecular-Weight Heparin With Unfractionated Heparin Acutely and With Placebo for 6 Weeks in the Management of Unstable Coronary Artery Disease

Fragmin in Unstable Coronary Artery Disease Study (FRIC)

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Abstract

Background Low-molecular-weight heparin has a number of pharmacological and pharmacokinetic advantages over unfractionated heparin that make it potentially suitable, when used in combination with aspirin, for the treatment of unstable coronary artery disease.

Method and Results Patients with unstable angina or non-Q-wave myocardial infarction (1482) were included in the study, which had two phases. In an open, acute phase (days 1 to 6), patients were assigned either twice-daily weight-adjusted subcutaneous injections of dalteparin (120 IU/kg) or dose-adjusted intravenous infusion of unfractionated heparin. In the double-blind, prolonged treatment phase (days 6 to 45), patients received subcutaneously either dalteparin (7500 IU once daily) or placebo. During the first 6 days, the rate of death, myocardial infarction, or recurrence of angina was 7.6% in the unfractionated heparin-treated patients and 9.3% in the dalteparin-treated patients (relative risk, 1.18; 95% confidence interval [CI], 0.84 to 1.66). The corresponding rates in the two treatment groups for the composite end point of death or myocardial infarction were 3.6% and 3.9%, respectively (relative risk, 1.07; 95% CI, 0.63 to 1.80). Revascularization procedures were undertaken in 5.3% and 4.8% of patients in unfractionated heparin and dalteparin groups, respectively (relative risk, 0.88; 95% CI, 0.57 to 1.35). Between days 6 and 45, the rate of death, myocardial infarction, or recurrence of angina was 12.3% in both the placebo and dalteparin groups (relative risk, 1.01; 95% CI, 0.74 to 1.38). The corresponding rates for death or myocardial infarction were 4.7% and 4.3% (relative risk, 0.92; 95% CI, 0.54 to 1.57). Revascularization procedures were undertaken in 14.2% and 14.3% of patients in the placebo and dalteparin groups, respectively.

Conclusions Our results add to previous evidence suggesting that the low-molecular-weight heparin dalteparin administered by twice-daily subcutaneous injection may be an alternative to unfractionated heparin in the acute treatment of unstable angina or non-Q-wave myocardial infarction. Prolonged treatment with dalteparin at a lower once-daily dose in our study did not confer any additional benefit over aspirin (75 to 165 mg) alone.

heparin angina myocardial infarction

In the treatment of unstable coronary artery disease, therapeutic-dose unfractionated heparin and aspirin are effective in reducing the adverse ischemic outcomes, including death and myocardial infarction.^{1 2 3 4} The combination of both drugs was found to be most effective.⁵ Unfractionated heparin has a number of limitations in this setting, however, and reactivation of disease or rebound hypercoagulability has been reported when the drug is discontinued after short-term therapy, although this may be prevented or reduced by the concomitant use of aspirin.⁶ Low-molecular-weight heparins have pharmacological and pharmacokinetic advantages over unfractionated heparin, including a predictable pharmacokinetic profile, high bioavailability, and long plasma half-life, all of which result in effective levels of anticoagulant activity after subcutaneous administration without laboratory monitoring.^{7 8} In addition, low-molecular-weight heparins have been found to be as effective or more effective than unfractionated heparin in the treatment of other thromboembolic disorders, including venous thromboembolism⁹ and ischemic stroke.¹⁰ Thus, low-molecular-weight heparins might also have the potential to improve the efficacy and safety of antithrombotic therapy in the management of unstable coronary artery disease.

In a recent study in acute unstable coronary artery disease (FRISC), the low-molecular-weight heparin dalteparin (120 IU/kg) administered twice daily subcutaneously with aspirin was shown to reduce the frequency of death and new myocardial infarction in the acute phase by 63% in comparison with aspirin alone.¹¹ The reduction in ischemic outcomes in this study was similar to that demonstrated in other smaller studies with adjusted therapeutic-dose intravenous unfractionated heparin,^{1 2 4 5} but large-scale comparisons of the two types of heparin in this indication have yet to be reported.

There are several reasons to believe that prolonged anticoagulant therapy might improve the outcome in unstable angina. First, the risk of ongoing or recurrent ischemia after acute presentation of unstable angina remains increased for 6 to 12 weeks.² Second, reactivation of the disease process may occur after cessation of short-term heparinization.⁶ Third, coagulant activity and thrombin generation in this group of patients are increased for several months after the acute event.^{12 13} Low-molecular-weight heparins have pharmacokinetic properties that allow long-term treatment through subcutaneous injection at home without monitoring and may be beneficial during a prolonged treatment phase.

The aims of this study were to compare the efficacy and safety of weight-adjusted subcutaneous dalteparin, administered twice daily, with those of intravenous unfractionated heparin in the acute treatment of unstable angina or non-Q-wave myocardial infarction and, primarily, to investigate the value of prolonged treatment with dalteparin at a lower dose in comparison with placebo in patients initially anticoagulated for a period of 5 to 8 days. All patients received aspirin throughout the study.

Methods

Study Design

The FRIC study was prospective, randomized, multinational, and parallel group in design and had two phases. In the acute phase, between days 1 and ≈6 after randomization, patients with unstable coronary artery disease received open treatment with either dalteparin, administered by twice-daily subcutaneous injection, or unfractionated heparin, administered at first by continuous intravenous infusion (for ≥48 hours) and then by subcutaneous injection. In the double-blinded prolonged-treatment phase, between days 6 and 45 after randomization, dalteparin, administered by once-daily subcutaneous injection, was compared with placebo. Randomization for each of the two phases was performed once at the beginning of the study.

Clinical follow-up and resting ECGs were undertaken in all patients at 3 months after randomization.

Eighty-one centers in nine countries (Austria, Canada, Germany, Italy, the Netherlands, Norway, Spain, UK, and the United States of America) participated in the study. Approval of the protocol was obtained at each center from the appropriate authority.

Patients

Consecutive male or female patients presenting with chest pain were potentially eligible for inclusion in the study if they satisfied the clinical criteria for unstable coronary artery disease according to a modified Braunwald classification.¹⁴ Admission to the study had to be within 72 hours of the last episode of chest pain, and the ECG on admission had to show either one or both of the following abnormalities in at least two adjacent leads: temporary or persistent ST-segment depression of ≥ 0.1 mV and/or temporary or persistent T-wave inversion of ≥ 0.1 mV below baseline without corresponding Q waves. Patients who subsequently had biochemical evidence of a non-Q-wave myocardial infarction remained eligible.

Patients were excluded if they had any of the following: newly developed Q waves; left bundle-branch block on ECG; an indication for thrombolytic therapy; a pacemaker; known primary myocardial disease, septic endocarditis, pericarditis, or aortic valvular disease of hemodynamic significance; any known defect of hemostasis; ongoing treatment with oral anticoagulants or heparin (if administered for >12 hours or if the total dose received was $>10\,000$ IU); diastolic blood pressure >120 mm Hg or systolic blood pressure <90 mm Hg; fever with temperature $\geq 39^\circ\text{C}$; hemoglobin <125 g/L if male or <110 g/L if female; known renal or liver insufficiency; a history of a cerebrovascular event, peptic ulceration, or gastrointestinal bleeding within 3 months of admission; surgery of any type within 1 week or eye or ear surgery or neurosurgery within 1 month of admission; malignancy or other diseases of unfavorable prognosis; or known hypersensitivity to aspirin, unfractionated heparin, or low-molecular-weight heparin.

Patients in whom PTCA or CABG was planned within 3 weeks of admission were also excluded, as were women who were pregnant or lactating and any person for whom the at-home administration of study treatment was likely to be difficult.

Eligible patients who gave their written informed consent were randomized at entry to treatment in both phases of the study. Instructions for treatment allocation during the open phase and coded treatment during the double-blinded phase were obtained for each patient by telephone from a randomization center in each country.

Treatment Regimens

Aspirin (75 to 165 mg/d) was started in all patients as soon as possible after admission to hospital and continued throughout the study. Other antianginal medications were administered according to the standard practice at each center.

Treatment was started as soon as possible after randomization and within 72 hours of the last episode of chest pain. In the open phase of the study, patients randomized to weight-adjusted low-molecular-weight heparin received dalteparin (120 IU/kg) by subcutaneous injection every 12 hours. Those randomized to unfractionated heparin received an initial intravenous bolus of 5000 IU followed, within 2 hours, by a continuous infusion at a rate of 1000 IU/h adjusted to maintain the aPTT at 1.5-fold the control value. The aPTT was measured 6 and 12 hours after the start of the infusion and daily thereafter. The infusion could be maintained throughout the acute phase or stopped after a minimum of 48 hours and replaced within 8 to 12 hours with a subcutaneous regimen of unfractionated heparin (12 500 IU every 12 hours).

Low-molecular-weight heparin (dalteparin [Fragmin], Pharmacia & Upjohn) was provided at a concentration of 10 000 IU/mL. Unfractionated heparin was provided by Pharmacia & Upjohn according to local preference.

In the second, double-blind phase of the study, dalteparin (7500 IU) or saline in prefilled syringes (0.3 mL) was administered subcutaneously in a fixed single-daily dose. Before discharge from hospital, all patients were instructed in the self-injection technique.

Outcomes

The principal outcomes of the study were death, myocardial infarction, and recurrence of angina during the double-blinded phase ($\approx$ days 6 to 45) of the study. The primary analysis of efficacy was a comparison of the composite of the principal outcomes between the two treatment groups. Only one outcome was counted for each patient; where two occurred, death was counted before myocardial infarction, and myocardial infarction was counted before recurrent angina.

A patient was considered to have had a myocardial infarction if the event was confirmed by serial ECG examination or if two of three other diagnostic criteria were met: prolonged ischemic chest pain, ECG evolution suggestive of myocardial infarction according to the Minnesota code, and elevation of relevant cardiac enzymes (CK-MB greater than the upper normal limit or total CK greater than twice the usual upper limit). (The final decision was made by the blinded Steering Committee, which did not include Pharmacia & Upjohn personnel.) In hospitalized patients, recurrence of angina was defined as any anginal chest pain that required a nitroglycerin infusion to be restarted. The decision was made by the treating physician. The episode had to be new and unrelated to the event that led to the inclusion of the patient in the study. In patients who had been discharged from hospital, recurrence of angina was defined as any new episode of angina requiring readmission to hospital and the institution of a nitroglycerin or heparin infusion.

The secondary outcomes were death, myocardial infarction, and recurrence of angina occurring in the acute phase of the study (before the first injection of dalteparin or placebo in the double-blinded phase), revascularization by PTCA or CABG during either phase of the study, and ischemia during exercise testing. The indications for angiography and revascularization were predetermined and were the same in all the study centers. Thus, angiography was indicated in all patients with refractory angina despite medication or significant ischemia or inadequate circulatory response during the initial exercise test evaluation. Revascularization was indicated in those patients subsequently shown to have left main vessel disease, three-vessel disease, left anterior descending coronary artery stenosis (75%), or disabling angina with significant coronary stenosis. Exercise tests were undertaken in all suitable patients at the end of the first and second phases of the study; these results will be reported separately.

Safety was also considered a secondary outcome; the main variables that were studied were major or minor bleeding, thrombocytopenia (platelet count $<100 \times 10^9/L$), and allergic reactions. A bleeding event was classified as major if it led to a fall in the hemoglobin level of ≥ 20 g/L, required transfusion, was intracranial, or caused death or cessation of the study treatment.

Additional Investigations

Resting ECG was performed before and 2 days after inclusion in the study. It was repeated at the end of the first (days 5 to 8) and second (day 45) phases of the study and after 3 months. Hemoglobin levels and platelet counts were measured according to a similar schedule. Serial cardiac enzymes (CK, CK-MB, ASAT according to local routine), serum creatinine, and the international normalized ratio (INR) were measured at the start of the study. Cardiac enzymes were also measured in the event of a new episode of angina or myocardial infarction. aPTT was measured according to the standard method of each study center and at the times previously described. Anti-factor Xa activity in patients receiving dalteparin in the acute phase was measured in blood samples taken before the injection and at 2 and ≈ 6 days after randomization for retrospective analysis.

Statistical Analysis

Sample sizes were based on the assumption that the composite incidence of the primary outcomes would be 10% in placebo-treated patients and 5% in dalteparin-treated patients during the prolonged treatment phase of the study (days 6 to 45). It was also assumed that 40% of patients would have a primary outcome or be withdrawn for some other reason in the first phase of the study and would not progress to the second phase. We therefore calculated that 1500 patients would need to be randomized to detect a treatment difference in a two-sided test with significance level of .05 and a power of .80. The trial did not have sufficient power to show equivalence of heparin and dalteparin in the acute phase.

Efficacy variables were analyzed according to the intention-to-treat principle, and 95% CIs were calculated for the incidence of all events. Treatment comparisons were made using the Cochran-Mantel-Haenszel test and Fisher's exact test. The time to occurrence of cardiac events was analyzed by a log rank test.

Results

Between March 1993 and April 1995, 1499 patients entered the study and were randomized to treatment in both phases. Of these, 17 were randomized but excluded from all subsequent analyses because they did not receive any study treatment. Of the remaining 1482 patients, 731 were assigned to initial treatment with unfractionated heparin and 751 were assigned to

receive dalteparin.

During the acute phase (days 1 to 6), 350 patients (166 in the dalteparin group and 184 in the heparin group) were withdrawn from the study on account of thrombolytic therapy (4 to 1) due to myocardial infarction, myocardial infarction (22 to 30) or need for heparin infusion (29 to 19), a serious adverse event (11 to 13), coronary revascularization (45 to 48), patient request (28 to 29), or other reasons (eg, intercurrent illness, epidural anesthesia, renal insufficiency) (27 to 40). Thus, 1132 patients entered the second, prolonged-treatment phase of the study, and 1126 were included in the intention-to-treat evaluation (562 in the dalteparin group and 564 in the placebo group). The characteristics of the patients (median age, 65 years) in the two treatment groups of each phase of the study were comparable at baseline (Table 1¹). Overall, 64% of patients were male and 36% were female. Eighty-four percent had unstable angina, and 16% had a non-Q-wave infarction. A history of hypertension or previous myocardial infarction was recorded in 39% and 25% of patients, respectively, and 56% of patients were receiving aspirin at entry. Current smokers represented 27% of the study population at baseline. During the acute phase, 56% of patients received a β -blocker; 52%, a calcium channel blocker; 70%, an oral nitrate; and 8%, digitalis. As stipulated in the protocol, all patients received aspirin.

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Table 1.

Baseline Characteristics of Patients in Each Phase of the Study

Characteristic	Phase 1		Phase 2	
	Unfractionated Heparin (n=731)	Dalteparin (120 IU/kg BID) (n=751)	Placebo (n=565)	Dalteparin (7500 IU OD) (n=567)
Median age (range), y	65 (25-89)	65 (29-92)	65 (31-88)	65 (25-89)
Male:female	66:34	63:37	64:36	64:36
Median body weight (range), kg	73 (45-153)	74 (42-118)	74 (42-153)	73 (44-125)
Median body mass index (range), kg/m ²	26 (18-46)	26 (17-42)	26 (17-46)	26 (19-42)
Inclusion criteria, %				
Angina (Braunwald class)				
I	30	33	30	32
II	11	13	11	13
III	42	38	42	42
Non-Q-wave infarction	16	16	17	13
ECG changes, %				

Characteristic	Phase 1		Phase 2	
	Unfractionated Heparin (n=731)	Dalteparin (120 IU/kg BID) (n=751)	Placebo (n=565)	Dalteparin (7500 IU OD) (n=567)
T-wave inversion	42	40	43	43
ST-segment depression	32	34	34	31
T-wave inversion+ ST-segment depression	25	25	23	26
Risk factor, %				
Current smoker	28	25	24	30
Hypertension	36	42	39	39
Diabetes mellitus	18	18	20	17
Previous myocardial infarction	22	27	24	21
Heart failure	9	9	9	9
Cerebrovascular disease	6	5	6	5
Peripheral arterial disease	10	8	8	9
Medication at entry, %				
Aspirin	55	57	55	57
β-Blocker	34	40	34	37
Ca ²⁺ channel blocker	37	40	37	38
Nitrate	38	42	37	39
Diuretic	16	18	17	16
Digitalis	10	10	10	10
ACE inhibitor	16	19	18	17

Acute Phase

During the first 6 days, comparable rates of the individual or combined outcomes of death, myocardial infarction, or recurrence of angina were observed in the two treatment groups (Table 2[¶]). The combined outcome occurred in 7.6% and 9.3% of patients treated with intravenous unfractionated heparin and dalteparin, respectively (relative risk, 1.18; 95% CI, 0.84 to 1.66). The corresponding rates of the composite of end point of death or myocardial infarction were 3.6% and 3.9% (relative risk, 1.07; 95% CI, 0.63 to 1.80). Revascularization procedures were undertaken in 5.3% of unfractionated heparin-treated and 4.8% of dalteparin-treated patients. The hazard curves showed no difference in the timing of the clinical outcomes in each group (Fig 1[¶]). *P* values are listed in Table 2[¶].

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Table 2.

Frequency of Death, Myocardial Infarction, and Recurrence of Angina (Need for Nitroglycerin Infusion) Within the First 6 Days

	Heparin (n=731)	Dalteparin (n=751)	Relative Risk	95% CI	<i>P</i>
Composite outcome, % (n)	7.6 (55)	9.3 (69)	1.18	0.84-1.66	.33
Death or myocardial infarction, % (n)	3.6 (26)	3.9 (29)	1.07	0.63-1.80	.80
Myocardial infarction, % (n)	3.2 (23)	2.6 (19)	0.81	0.45-1.48	.50
Nitrate infusion, % (n)	5.4 (39)	6.0 (45)	1.09	0.72-1.64	.70
Death, % (n)	0.4 (3)	1.5 (11)	3.37	1.01- 11.24	.05
Revascularization, % (n)	5.3 (39)	4.8 (36)	0.88	0.57-1.35	.55

Composite outcome is death, myocardial infarction, or recurrent angina.

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Figure 1.

Top, Occurrence of the composite outcome of death, myocardial infarction, and recurrence of angina in the acute phase.

Bottom, Occurrence of the composite outcome of death and myocardial infarction in the acute phase.

Adverse events during the acute phase were rare and are summarized in Table 3^{||}.

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Table 3.

Adverse Events Occurring During Phase 1 (Days 1 to 6) and Phase 2 (Days 6 to 45)

Prolonged-Treatment Phase

Between days 6 and 45, the frequency of the combined clinical outcomes of death, myocardial infarction, or recurrence of angina was 12.3% in both treatment groups (relative risk, 1.01; 95% CI, 0.74 to 1.38) (Table 4^{||}). The frequencies of the individual outcomes were also similar. The composite end point of death or myocardial infarction occurred in 4.7% and 4.3% of patients assigned to receive placebo and dalteparin, respectively (relative risk, 0.92; 95% CI, 0.54 to 1.57). Revascularization procedures were undertaken in ≈14% of patients in each group.

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Table 4.

Frequency of Death, Myocardial Infarction, and Recurrence of Angina (Need for Nitroglycerin or Heparin Infusion) in Days 6 to 45

	Placebo (n=561)	Dalteparin (n=562)	Relative Risk	95% CI	P
Composite outcome, % (n)	12.3 (69)	12.3 (69)	1.01	0.74- 1.38	.96
Death or myocardial infarction, % (n)	4.7 (26)	4.3 (24)	0.92	0.54- 1.57	.76
Myocardial infarction, % (n)	3.6 (20)	3.1 (17)	0.92	0.59- 1.72	.80
Recurrence of angina, % (n)	10.3 (57)	10.8 (60)	1.09	0.77- 1.54	.64
Death, % (n)	2.0 (11)	2.0 (11)	0.89	0.40- 2.02	.79
Revascularization, % (n)	14.2 (76)	14.3 (76)	1.01	0.75- 1.36	.97

Composite outcome was death, myocardial infarction, or recurrent angina.

The hazard curves showed no difference throughout the 6-week period in the occurrence of death or myocardial infarction or the recurrence of angina in the two groups (Fig 2 $\downarrow$).

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Figure 2.

Top, Occurrence of the composite outcome of death, myocardial infarction, and recurrence of angina in the prolonged-treatment phase. Bottom, Occurrence of the composite outcome of death and myocardial infarction in the prolonged-treatment phase.

The similarity of the event rates in the two treatment groups was consistent across all the predefined subgroups, including those with non-Q-wave infarction, smokers, and nonsmokers (Table 5^{||}).

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Table 5.

Frequency of Death, Myocardial Infarction, and Recurrence of Angina in the Predefined Subgroups During Days 6 to 45

Subgroup	Placebo (n=561)	Dalteparin (n=562)	Relative Risk	95% CI	P
Male, %	11.5	12.2	1.07	0.70- 1.64	.74
Female, %	13.7	12.5	0.88	0.53- 1.47	.63

Subgroup	Placebo (n=561)	Dalteparin (n=562)	Relative Risk	95% CI	P
Age, y					
≤70	11.2	10.5	0.95	0.63- 1.42	.80
>70	15.2	17.1	0.96	0.55- 1.68	.88
Smoker, %					
Smoker, %	11.0	7.6	0.78	0.35- 1.76	.55
Nonsmoker, %	12.7	14.3	1.16	0.83- 1.63	.39
Unstable angina, %					
Unstable angina, %	11.7	11.7	1.00	0.71- 1.42	1.00
Non-Q-wave myocardial infarction, %					
Non-Q-wave myocardial infarction, %	13.8	14.9	1.20	0.57- 2.57	.63
Body mass index, kg/m ²					
≤26	13.3	15.7	1.20	0.78- 1.84	.42
>26	11.4	8.4	0.81	0.48- 1.37	.43
Weight, %					
≤70 kg	13.4	16.7	1.13	0.72- 1.78	.59
>70 kg	11.4	8.5	0.74	0.46- 1.19	.22
Braunwald class, %					
I	14.0	11.9	0.84	0.46- 1.53	.56
II	12.9	8.3	0.74	0.34- 1.57	.43
III	9.8	12.7	1.32	0.79- 2.20	.29

Subgroup	Placebo (n=561)	Dalteparin (n=562)	Relative Risk	95% CI	P
Aspirin, %					
≤125 mg/d	11.2	10.9	0.94	0.62- 1.44	.79
>125 mg/d	14.2	15.0	1.04	0.64- 1.69	.88
Preheparin, %					
Yes	13.7	15.3	1.15	0.61- 2.20	.66
No	12.6	12.4	0.96	0.65- 1.42	.86
Not in high risk			0.94	0.55- 1.60	.81
In high risk			1.01	0.67- 1.51	.98

As in the acute phase, adverse events occurred infrequently (Table 3^{¶¶}). The two groups differed only in the frequency of minor bleeding events; these occurred in 2.8% of the patients receiving placebo compared with 5.1% of those receiving dalteparin. No patient in either group developed thrombocytopenia in this phase of the study.

The results of the exercise tests will be reported elsewhere.

Compliance and Withdrawals

Compliance during the prolonged-treatment phase with the once-daily injection of either dalteparin or placebo was good. The median number of self-administered injections recorded during this period was 38 (range, 0 to 50) in the placebo group and 38 (range, 0 to 52) in the dalteparin group. In total, 27 patients withdrew from the study between days 6 and 45 at their own request, of whom 19 and 8 had been assigned to dalteparin and placebo, respectively. Other reasons accounted for the withdrawal of an additional 50 patients (27 on dalteparin and 23 on heparin), mostly minor adverse events such as hematoma.

Anti-Factor Xa Activity and aPTT Values in the Acute Phase

The median preinjection anti-factor Xa activity in the dalteparin-treated patients was 0.35 IU/mL (range, 0.0 to 1.50) on day 2 and 0.37 (range, 0.00 to 1.46) on day 6.^{5 6 7 8} Of the patients assigned unfractionated heparin in the acute phase, 21% received an intravenous infusion throughout, whereas 79% went on to receive subcutaneous injections at a mean time of 57 hours after the initial infusion.

Discussion

The approach to treatment in the present study was the conservative one outlined in treatment guidelines that were prevalent when the study was started.¹⁴ Thus, although our purpose was to compare dalteparin and unfractionated heparin in the acute phase and dalteparin and placebo in the prolonged-treatment phase, patients considered to be at high risk of death or myocardial infarction underwent PTCA or CABG at any time, at the discretion of the local investigator. During the study, $\approx 7\%$ of the patients died or had an acute myocardial infarction, with approximately half of these events occurring during the acute phase and half during the subsequent 5 weeks. Revascularization procedures were undertaken in $\approx 15\%$ of the entire population. Whether a greater readiness to undertake PTCA or CABG in this group of patients would result in a lower rate of serious complications is being debated currently but no large-scale comparisons of the conservative and aggressive strategies have been reported.

The frequency of the combined clinical outcome of death, myocardial infarction, and recurrence of angina was similar during 6 days of treatment with either dalteparin (120 IU/kg twice daily) or aPTT-monitored intravenous unfractionated heparin, and the rates of revascularization procedures in the two groups were comparable. In view of the relatively small number of deaths in either group, the marginally significant excess early mortality with dalteparin was, in our opinion, probably a chance finding. Therefore, although not dimensioned to show equivalence of these two anticoagulant regimens in the acute phase, this study supports the evidence suggesting that body weight-adjusted low-molecular-weight heparins administered subcutaneously twice daily can be used as an alternative to intravenous unfractionated heparin in this indication.¹⁵ This is an important practical advance over current therapy. Low-molecular-weight heparins can be administered subcutaneously to give a predictable anticoagulant response without laboratory monitoring. Thus, they have the potential to markedly improve the clinical utility of anticoagulant therapy.

In the prolonged-treatment phase, between days 6 and 45, the frequency of the combined outcome of death, myocardial infarction, or recurrence of angina was similar in both dalteparin- and placebo-treated patients, a finding that was consistent across all the predefined subgroups, including those with or without non-Q-wave infarction, smokers, and nonsmokers. There were no differences between the two treatment groups in the rates of revascularization procedures.

Given the clear added benefit over aspirin alone of initial anticoagulation with either unfractionated or low-molecular-weight heparin in patients with unstable coronary artery disease^{1 2 6 11} and evidence that the underlying lesion remains active with accompanying thrombin generation for several weeks after the initial event,^{2 12 13} the reason for the apparent lack of benefit of prolonged treatment with low-molecular-weight heparin in this study is unclear. It is possible that after initial treatment with aspirin plus unfractionated heparin or low-molecular-weight heparin, continued treatment with aspirin may be sufficient to prevent important clinical outcomes in a low risk subset of patients—an inevitable feature of the conservative strategy used in this study was that high-risk patients were filtered out during the acute phase. This would seem unlikely, however, as aspirin has no direct effect on thrombin generation or action.

Another explanation is that the dose of low-molecular-weight heparin used in the prolonged-treatment phase of our study was too low or the interval between injections was too long to provide 24-hour anticoagulant cover. When this study was designed, it was hypothesized that thrombotic activity associated with acute unstable coronary artery disease decreased after the acute phase and that lower doses of anticoagulant would suffice. Our results indicate that this is not the case and that periods of inadequate anticoagulant activity in some patients might have permitted the reemergence of thrombosis. In FRISC, prolonged treatment with dalteparin led to a trend toward reduced death and myocardial infarction even when the dose of dalteparin was reduced to half that which was found to be effective in the acute phase.¹¹ It is possible, however, that greater benefits would have been observed if weight-adjusted twice-daily dalteparin had also been used for the prolonged treatment. This is supported by the results of a study of low-molecular-weight heparin in ischemic stroke in which greater efficacy was achieved with twice-daily than with once-daily dosing.¹⁰

How patients would view twice-daily injections is open to speculation, although compliance with the once-daily regimen used in this study was excellent. This suggests that a future study with higher and more frequent doses of dalteparin is at least feasible.

Study Limitations

It should be stated that the trial was not powered to detect a difference between heparin and dalteparin in the acute phase. Furthermore, this part of the study was not blinded. However, the almost identical incidence of recurrent angina, myocardial infarction, and need for revascularization in both groups (Table 2¹¹) strongly suggests equivalence of both treatment regimens, despite a borderline difference in mortality. Intravenous heparin obviously is very effective in acute coronary syndromes but is usually discontinued after 48 to 72 hours, whereas there clearly is ongoing risk for cardiovascular complications for ≥ 7 days.

Conclusions

The present study indicates that the low-molecular-weight heparin dalteparin administered by twice-daily subcutaneous injection is a safe and effective alternative to unfractionated heparin in the acute treatment of unstable coronary heart disease. There is, however, no evidence from this study that prolonged treatment with dalteparin at a reduced dose in addition to aspirin confers any additional benefit over aspirin alone. These data do not preclude a benefit to prolonged treatment with a more intense level of anticoagulation.

Investigators

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Selected Abbreviations and Acronyms

aPTT = activated partial thromboplastin time

CABG = coronary artery bypass graft surgery

CI	=	confidence interval
FRIC	=	Fragmin in Unstable Coronary Artery Disease Study
FRISC	=	Fragmin During Instability in Unstable Coronary Artery Disease Study
PTCA	=	percutaneous transluminal coronary angioplasty

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