

## EFFECTS OF A LOW-MOLECULAR-WEIGHT HEPARIN ON THROMBUS REGRESSION AND RECURRENT THROMBOEMBOLISM IN PATIENTS WITH DEEP-VEIN THROMBOSIS

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### ABSTRACT

**Background** Low-molecular-weight heparins are frequently used to treat venous thromboembolism, but optimal dosing regimens and clinical outcomes need further definition.

**Methods** In this multicenter, open-label study with blinded adjudication of end points, we randomly assigned patients with acute deep-vein thrombosis to one of three treatment regimens: intravenous administration of unfractionated heparin; subcutaneous administration of a low-molecular-weight heparin, reviparin, twice a day for one week; or subcutaneous administration of reviparin once a day for four weeks. The primary end point was evidence of regression of the thrombus on venography on day 21; secondary end points were recurrent venous thromboembolism, major bleeding within 90 days after enrollment, and death.

**Results** Of the patients receiving unfractionated heparin, 40.2 percent (129 of 321) had thrombus regression, as compared with 53.4 percent (175 of 328) of the patients receiving reviparin twice daily and 53.5 percent (167 of 312) of the patients receiving reviparin once daily. With regard to thrombus regression, reviparin administered twice daily was significantly more effective than unfractionated heparin (relative likelihood of thrombus regression, 1.28; 97.5 percent confidence interval, 1.08 to 1.52), as was reviparin administered once daily (relative likelihood, 1.29; 97.5 percent confidence interval, 1.08 to 1.53). Mortality and the frequency of episodes of major bleeding were similar in the three groups.

**Conclusions** In acute deep-vein thrombosis, reviparin regimens are more effective than unfractionated heparin in reducing the size of the thrombus. Reviparin is also more effective than unfractionated heparin for the prevention of recurrent thromboembolism and equally safe. (N Engl J Med 2001;344:626-31.)

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**I**MMEDIATE anticoagulation is considered the treatment of choice for deep-vein thrombosis or pulmonary embolism. This is usually accomplished by the administration of unfractionated heparin for five to seven days,<sup>1-3</sup> at a dose that is monitored to achieve an activated partial-thromboplastin time of 1.5 to 2.5 times the base-line value.<sup>4</sup> Treatment with vitamin K antagonists is usually initiated at the same time as treatment with unfractionated heparin. The objective of this "standard treatment" is to prevent pulmonary embolism, the recurrence of deep-vein thrombosis, and propagation of thrombus.

Because of their greater bioavailability, low-molecular-weight heparins can be administered subcutaneously without the need for laboratory monitoring. Randomized, controlled trials of treatment for acute deep-vein thrombosis<sup>5-20</sup> or pulmonary embolism<sup>21</sup> have demonstrated that low-molecular-weight heparins are at least as effective and safe as unfractionated heparin. In addition to the assessments of clinical outcome, repeated venography has revealed a tendency for the thrombus to regress in the groups receiving a low-molecular-weight heparin.<sup>5,10,11,14</sup> Although these studies did not have the statistical power to show the superiority of low-molecular-weight heparins over unfractionated heparin for improving venous patency, meta-analyses concluded that treatment with a low-molecular-weight heparin increased the frequency of thrombus regression.<sup>22-24</sup>

A definition of a response to therapy on venography (a reduction of at least 30 percent in the Marder score<sup>25</sup>) was used recently to compare the efficacy of a low-molecular-weight heparin with that of unfractionated heparin.<sup>26</sup> A correlation between the clinical rate of recurrence and the rate of thrombus regression was not achieved.

Therefore, we conducted a study comparing two regimens of the low-molecular-weight heparin reviparin with a regimen of unfractionated heparin, using both clinical recurrence of venous thromboembolism and thrombus regression, as assessed by venography, as outcome measures. Instances of major bleeding and deaths from any cause were recorded throughout the study.

### METHODS

#### Study Design

In a multicenter, randomized, controlled, open-label trial with blinded assessment of outcomes, the intravenous administration of unfractionated heparin for 5 to 7 days was compared with the subcutaneous administration of reviparin twice a day for 5 to 7 days or once a day for 28±2 days. All the patients received vitamin K antagonists until the end of the 90-day observation period. A total of 104 centers in 10 countries participated in the study (see the Appendix). The protocol was approved by the local institutional review boards and was conducted in accordance with national and international regulations.

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\*Other members of the CORTES (Clivarin: Assessment of Regression of Thrombosis, Efficacy, and Safety) study group are listed in the Appendix.

## Patients

Patients who were at least 18 years of age and had acute deep-vein thrombosis of the legs, confirmed by venography, and who had had symptoms for no more than 14 days were eligible for enrollment. All patients gave written informed consent. Criteria for exclusion from the study were the presence of thrombi only in isolated calf veins or isolated muscle veins; clinically symptomatic pulmonary embolism; treatment with unfractionated heparin, a low-molecular-weight heparin, or a vitamin K antagonist for 24 hours or more before enrollment; uncontrolled hypertension; stroke within three weeks before enrollment; cerebral vascular aneurysm or active gastroduodenal ulcer; bacterial endocarditis; thrombocytopenia (less than 100,000 platelets per cubic millimeter); severe liver or renal insufficiency; receipt of spinal or epidural anesthesia or lumbar puncture in the five days before enrollment; surgery in the five days before enrollment; concomitant treatment with fibrinolytic agents or platelet-function inhibitors; a body weight of less than 35 kg; pregnancy; and known drug abuse.

## Treatments

Patients were randomly assigned to one of three groups, stratified according to site. The first group received an intravenous bolus of 5000 IU of unfractionated heparin, followed by a continuous intravenous infusion of 1250 IU per hour. The second group received the low-molecular-weight heparin reviparin (Clivarin, Knoll, Ludwigshafen, Germany) twice a day for five to seven days. In both these groups, a vitamin K antagonist was given from day 1 to day 90. The third group received reviparin once a day for 28 days and a vitamin K antagonist from day 21 to day 90. The dose of reviparin, given as one injection every 12 hours or as one injection every 24 hours, was based on the patient's weight (7000 anti-Xa units for a weight of 35 to 45 kg, 8400 anti-Xa units for 46 to 60 kg, and 12,600 anti-Xa units for more than 60 kg).

The intravenous infusion of unfractionated heparin was adjusted according to daily measurements of the activated partial-thromboplastin time to achieve a value 1.5 to 2.5 times the base-line level. Heparin treatment was continued until an international normalized ratio of more than 2 was reached, and this ratio was subsequently maintained.

## End Points

The primary outcome variable with respect to efficacy was a change in the venographically determined thrombus size between base line and day 21 ( $\pm 2$  days), assessed with the use of the Marder score.<sup>25</sup> This score allocates points to each of the involved deep venous segments of the lower limb. If all the veins in one leg are occluded, the total score is 40 (6 for iliac, 4 for common femoral, 10 for superficial femoral, 4 for popliteal, 4 for anterior tibial, 6 for peroneal, and 6 for posterior tibial veins). Partially occluded veins are given a lower score, depending on the extent of the thrombus. Patients were considered to have a response when their scores decreased by at least 30 percent; all other patients were classified as having no response, including those in whom new, confirmed symptomatic venous thromboembolism developed. This reduction in the Marder score was selected because it has been shown to represent partial treatment success accurately. The venograms were assessed by two members of an independent committee who were unaware of the patients' treatment assignments and of whether the venograms were obtained before or after treatment. Discrepancies were resolved by a joint evaluation. The number of patients whose Marder scores decreased was also assessed. Symptomatic deep-vein thrombosis and pulmonary embolism were documented by objective methods during the 90-day observation period; these clinical variables and death were selected as secondary end points, and events were also reviewed by an adjudication committee whose members were unaware of the patients' treatment assignments.

## Assessment of Clinical Outcomes

Immediate venography or scintigraphy was requested if clinical symptoms of recurrent deep-vein thrombosis or pulmonary em-

bolism developed, according to predefined criteria. The criteria for the verification of symptomatic deep-vein thrombosis were an extension of an intraluminal filling defect visible on a venogram, a new intraluminal filling defect, or an extension of the area of nonvisualization of proximal veins plus a sudden cutoff defect visible on a venogram in at least two projections.

The criteria for the diagnosis of symptomatic pulmonary embolism were a ventilation-perfusion mismatch of at least 75 percent of the segmental size, positive results on pulmonary angiography, or a finding of pulmonary embolism at autopsy. If no adequate objective tests were available, the adjudication committee based its final decision on the clinical information provided.

## Adverse Events

Bleeding complications and other adverse events were evaluated by an independent safety committee whose members were unaware of the patients' treatment assignments. Bleeding was defined as major if it was clinically overt and associated with a fall in the hemoglobin level of at least 2.0 g per deciliter, if it required the transfusion of two or more units of red cells, if it was retroperitoneal or intracranial, or if it warranted the permanent discontinuation of treatment. For patients who died, the cause of death was classified as pulmonary embolism, hemorrhage, cancer, or other.

## Laboratory Tests

Deep-frozen, platelet-poor plasma was analyzed at a central laboratory. Each center monitored the dosage of unfractionated heparin with use of the local reagent used for determining the activated partial-thromboplastin time. Anti-factor Xa activity was measured centrally with the use of an amidolytic assay.

Complete blood counts were obtained before enrollment; platelet counts were performed on days 4, 8, 14, and 21.

## Statistical Analysis

Well-documented methods of determining sample size<sup>27</sup> were used to ensure that the study would have at least 80 percent statistical power for the two major objectives: to show that reviparin administered twice daily for one week is not inferior to unfractionated heparin and that reviparin administered once daily for four weeks is superior to unfractionated heparin for the treatment of deep-vein thrombosis. Assuming a 30 percent rate of refusal to undergo follow-up venography or other major violations of the protocol, a total of 1134 patients (378 per group) were needed.

The Mantel-Haenszel statistic was used according to the method of Yanagawa<sup>28</sup> to compare reviparin administered twice daily with unfractionated heparin and reviparin administered once daily with unfractionated heparin. To ensure an overall alpha level of 0.05, a closed testing procedure was used; in the first step, the hypothesis that twice-daily reviparin is not inferior to unfractionated heparin was tested at the 0.025 level (the noninferiority test).

With regard to recurrent venous thromboembolism, the limit of noninferiority of twice-daily reviparin was defined by an incidence rate no more than 3 percentage points higher than that in the group receiving unfractionated heparin. This hypothesis of noninferiority was tested according to the method of Blackwelder.<sup>29</sup> The superiority of once-daily reviparin over unfractionated heparin was determined by the Mantel-Haenszel test. The same procedure was used to ensure an overall alpha level of 0.05. Except for those calculated by the noninferiority test, all reported P values are two-sided. All treatment effects were described as differences in incidence and estimates of relative risk with two-sided 97.5 percent confidence intervals.

## RESULTS

### Base-Line Characteristics

The study was carried out between July 1996 and November 1998. A total of 2607 consecutive patients with symptomatic acute deep-vein thrombosis

of the leg, confirmed by venography, were screened, and 1148 were enrolled. Eleven enrolled patients never received study medication and were not included in the analysis; thus, the study population consisted of 1137 patients. A total of 375 patients were assigned to receive unfractionated heparin, 388 to receive rivarparin twice daily, and 374 to receive rivarparin once daily; of these, 961 had two venograms that could be evaluated (321, 328, and 312 patients, respectively). There were no significant differences between the treatment groups with regard to base-line characteristics (Table 1).

### Efficacy

The proportions of patients who responded to treatment according to the venographic criteria were 40.2 percent (129 of 321) in the group receiving unfractionated heparin, 53.4 percent (175 of 328) in the group receiving rivarparin twice daily, and 53.5 percent (167 of 312) in the group receiving rivarparin once daily. The superiority of rivarparin administered twice daily ( $P < 0.001$ ) and the superiority of rivarparin administered once daily ( $P < 0.001$ ), as compared with unfractionated heparin, were demonstrated. Rivarparin administered twice daily was significantly superior to

unfractionated heparin (relative likelihood of regression of thrombus, 1.28; 97.5 percent confidence interval, 1.08 to 1.52), as was rivarparin administered once daily (relative likelihood, 1.29; 97.5 percent confidence interval, 1.08 to 1.53) (Table 2).

Recurrent thromboembolic events occurred in 7 of 388 patients (1.8 percent) receiving rivarparin twice daily (relative risk of recurrence, 0.28; 97.5 percent confidence interval, 0.11 to 0.74) and in 13 of 374 patients (3.5 percent) receiving rivarparin once daily (relative risk, 0.55; 97.5 percent confidence interval, 0.24 to 1.16), as compared with 24 of 375 patients (6.4 percent) receiving unfractionated heparin (Table 3). Since the upper limit of the 97.5 percent confidence interval for the difference was less than 0, rivarparin administered twice daily was significantly more effective than unfractionated heparin. Rivarparin administered once daily and unfractionated heparin did not differ significantly with regard to recurrent thromboembolic events ( $P = 0.07$ ).

There was a high degree of statistical correlation ( $P < 0.001$ ) between venographic results and clinical recurrence. Among 490 patients classified as having no response on venography, 34 (7.0 percent) had a recurrent venous thromboembolic event, whereas only 5 (1.0 percent) of 476 patients classified as having a response had such an event. A plot of the time to a recurrent event in the three treatment groups is shown in Figure 1.

The target range for the activated partial-thromboplastin time was reached in 67 percent of the patients treated with unfractionated heparin within 24 to 48 hours. The international normalized ratio reached the therapeutic range on day 5 in the group receiving unfractionated heparin and in the group receiving rivarparin twice daily. In the group receiving rivarparin once daily, oral anticoagulant therapy was initiated on day 22 and reached therapeutic levels on day 30.

### Safety

Major hemorrhagic complications occurred during the first 21 days in two patients receiving unfractionated heparin, in one patient receiving rivarparin twice daily, and in one patient receiving rivarparin once daily (Table 4). During the observation period from day 22 to day 90, two patients receiving rivarparin twice daily and one patient receiving rivarparin once daily had major bleeding. There were minor bleeding episodes during the first 21 days in 16 patients receiving unfractionated heparin, 13 patients receiving rivarparin twice daily, and 15 patients receiving rivarparin once daily. During days 22 to 90, there were 10 episodes of minor bleeding among patients receiving unfractionated heparin, 11 among those receiving rivarparin twice daily, and 9 among those receiving rivarparin once daily. The incidence of bleeding was similar in the three treatment groups (Table 4).

During the 90-day study period, 11 patients receiv-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	UNFRACTIONATED HEPARIN (N=375)	REVIPARIN TWICE DAILY (N=388)	REVIPARIN ONCE DAILY (N=374)
Male sex — no. (%)	206 (54.9)	214 (55.2)	201 (53.7)
Age — yr	58.6±0.83	58.6±0.78	58.5±0.80
Weight			
35–45 kg — no.	1	4	4
46–60 kg — no.	47	32	33
>60 kg — no.	326	350	337
Data missing — no.	1	2	0
Mean	78.8±0.81	78.5±0.78	78.8±0.80
Height — cm	170.5±0.48	170.3±0.46	170.2±0.49
Body-mass index†	27.0±0.25	27.1±0.24	27.3±0.25
Risk factors — no. (%)			
Recent surgery	4 (1.1)	1 (0.3)	6 (1.6)
Recent trauma	39 (10.4)	52 (13.4)	47 (12.6)
Recent immobilization	62 (16.5)	77 (19.8)	77 (20.6)
Recent childbirth‡	3 (1.8)	1 (0.6)	5 (2.9)
Use of oral contraceptives‡	15 (8.9)	16 (9.2)	12 (6.9)
Varicose veins	90 (24.0)	108 (27.8)	98 (26.2)
Known cancer	42 (11.2)	41 (10.6)	54 (14.4)
History of deep-vein thrombosis	67 (17.9)	72 (18.6)	77 (20.6)
History of pulmonary embolism	18 (4.8)	14 (3.6)	21 (5.6)
Congenital thrombophilia	10 (2.7)	7 (1.8)	9 (2.4)
Other thrombophilia§	14 (3.7)	10 (2.6)	6 (1.6)

\*Plus-minus values are means ±SE.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Percentages are for women only.

§Values indicate the incidence of thrombophilia as judged by the treating physician.

**TABLE 2.** VENOGRAPHIC ASSESSMENT OF THE THREE TREATMENT GROUPS.

ASSESSMENT	UNFRACTIONATED HEPARIN	REVIPARIN TWICE DAILY*	REVIPARIN ONCE DAILY†
	number (percent)		
Randomized patients	375	388	374
Patients with 2 venograms	321	328	312
Patients with a response‡	129 (40.2)	175 (53.4)	167 (53.5)
Patients with no response	192 (59.8)	153 (46.6)	145 (46.5)
No relevant change§	167 (52.0)	140 (42.7)	128 (41.0)
Deterioration¶	25 (7.8)	13 (4.0)	17 (5.4)

\*For twice-daily reviparin as compared with unfractionated heparin, the relative likelihood of regression of thrombus was 1.28 (97.5 percent confidence interval, 1.08 to 1.52;  $P < 0.001$ ).

†For once-daily reviparin as compared with unfractionated heparin, the relative likelihood of regression of thrombus was 1.29 (97.5 percent confidence interval, 1.08 to 1.53;  $P < 0.001$ ).

‡Patients with a response were defined as those with a decrease of at least 30 percent in their Marder score.

§Values are for patients with no change or with an absolute increase or decrease of no more than 29 percent in the Marder score.

¶Values are for patients with an increase of at least 30 percent in the Marder score.

ing unfractionated heparin died, as did 9 receiving reviparin twice daily and 15 receiving reviparin once daily. A total of 6 of 42, 5 of 41, and 9 of 54 patients with cancer died in the groups receiving unfractionated heparin, reviparin twice daily, and reviparin once daily, respectively (Table 4). Two patients receiving unfractionated heparin, none receiving reviparin twice daily, and two receiving reviparin once daily had heparin-associated thrombocytopenia, defined as a platelet count below 100,000 per cubic millimeter or a drop of more than 50 percent in the platelet count during administration of the drug. Pulmonary embolism developed in one of the patients who had thrombocytopenia two days after the discontinuation of unfractionated heparin; by this time, his platelet count had returned to normal.

## DISCUSSION

Our study demonstrates that two regimens of a low-molecular-weight heparin, reviparin, are more effective than a regimen of unfractionated heparin for the initial treatment of deep-vein thrombosis, as assessed by a greater reduction in thrombus size on sequential venography. The clinical end points, recurrent deep-vein thrombosis and new pulmonary embolism, were also less frequent in the two groups receiving reviparin, and this reduction in clinical events was significantly correlated with the venographic results.

The clinical and venographic results were similar in the groups receiving reviparin twice daily and once daily; once-daily reviparin was given without a vitamin K antagonist for the first 21 days and thus could

**TABLE 3.** CLINICAL END POINTS.

END POINT	UNFRACTIONATED HEPARIN (N=375)	REVIPARIN TWICE DAILY* (N=388)	REVIPARIN ONCE DAILY† (N=374)
	number (percent)		
Suspected end point			
Deep-vein thrombosis	16	12	9
Pulmonary embolism	19	14	15
Confirmed end point			
Recurrent deep-vein thrombosis or pulmonary embolism	24 (6.4)	7 (1.8)	13 (3.5)
Deep-vein thrombosis	11 (2.9)	4 (1.0)	6 (1.6)
Pulmonary embolism	13 (3.5)	2 (0.5)	6 (1.6)
Deep-vein thrombosis and pulmonary embolism	0	1 (0.3)	1 (0.3)

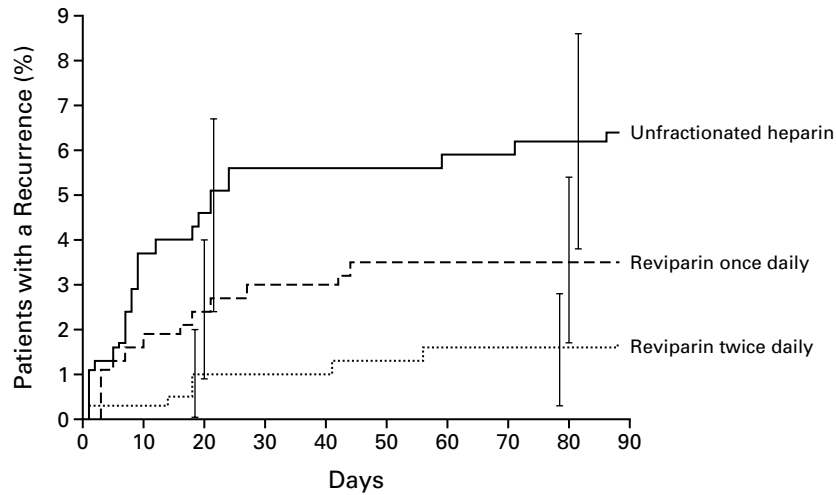
\*For twice-daily reviparin as compared with unfractionated heparin, the relative risk of recurrence was 0.28 (97.5 percent confidence interval, 0.11 to 0.74;  $P < 0.001$ ) (absolute difference, -4.60 percent; 97.5 percent confidence interval, -7.81 to -1.38 percent).

†For once-daily reviparin as compared with unfractionated heparin, the relative risk of recurrence was 0.55 (97.5 percent confidence interval, 0.24 to 1.16;  $P = 0.07$ ) (absolute difference, -2.92 percent; 97.5 percent confidence interval, -6.46 to 0.62 percent).

be a safe and effective alternative for patients with a contraindication to oral anticoagulant therapy.

The primary objective of anticoagulant therapy for deep-vein thrombosis is the prevention of fatal pulmonary embolism. However, the use of this end point in clinical trials is impractical because of the large number of patients who would need to be enrolled, and symptomatic recurrences of deep-vein thrombosis or nonfatal symptomatic pulmonary embolism are therefore frequently used to compare treatment effects. Clinically detected new symptomatic thromboses are encountered less frequently than recurrent thrombosis, which is detected by venography, after initial treatment, as is well demonstrated in trials of prevention of thrombosis in patients at high risk.<sup>30-32</sup> This discrepancy is even more pronounced with regard to pulmonary embolism. Up to 50 percent of patients with an acute deep-vein thrombosis have asymptomatic pulmonary embolism at presentation.<sup>26,33</sup> Subsequent symptoms of pulmonary embolism during treatment may be due to a preexisting pulmonary embolism rather than to new disease. It is thus inappropriate to rely on clinical end points alone to assess the efficacy of therapy for deep-vein thrombosis.

The venographic assessment of the change in thrombus size over time is a surrogate marker for regression, but it permits the evaluation of treatment effects in every patient with two venograms. The use of a venographic score,<sup>25</sup> which allows for definitions of regression, progression, and unchanged thrombosis, ensures an objective evaluation. The definition of response to therapy (a reduction of at least 30 per-



NO. AT RISK									
	375	360	355	351	349	348	347	347	346
Unfractionated heparin	375	366	361	358	356	354	354	352	350
Reviparin once daily	388	387	383	382	380	379	377	375	374

**Figure 1.** Kaplan–Meier Analysis of the Time to the Recurrence of Thromboembolic Events over a Period of 90 Days in the Three Treatment Groups.

I bars represent 95 percent confidence intervals at 20 and 80 days.

**TABLE 4.** ADVERSE EVENTS.

ADVERSE EVENT	UNFRACTIONATED HEPARIN (N=375)	REVIPARIN TWICE DAILY (N=388)	REVIPARIN ONCE DAILY (N=374)
	number (percent)		
Bleeding event			
Days 0–21			
Major bleeding	2 (0.5)	1 (0.3)	1 (0.3)
Minor bleeding	16 (4.3)	13 (3.4)	15 (4.0)
Days 22–90			
Major bleeding	0	2 (0.5)	1 (0.3)
Minor bleeding	10 (2.7)	11 (2.8)	9 (2.4)
Total (any bleeding)	28 (7.5)	27 (7.0)	26 (7.0)
Cause of death up to day 90			
Pulmonary embolism	2	1	2
Cancer and pulmonary embolism	1	0	1
Cancer	5	5	8
Other (e.g., cardiac failure, septicemia)	3	3	4
Total	11	9	15

cent in the Marder score) has been used in previous studies and has thus been validated.<sup>26,34</sup> Our study revealed a correlation between clinical outcome and change in thrombus size. The rate of venographically determined response can therefore be used confidently as a more objective way of assessing the efficacy of antithrombotic agents than reliance on clinical symptoms. Our data also reveal that patients without a venographically evident response to therapy are at

higher risk for symptomatic deep-vein thrombosis and pulmonary embolism.

The degree of regression of the thrombus may depend on the duration of treatment.<sup>26,34</sup> In a trial in which venography was performed after 14 days,<sup>26</sup> the response rate was 33 percent in the group assigned to unfractionated heparin and 42 percent in the group assigned to low-molecular-weight heparin. In the present trial, in which the venograms were obtained on day 21, the response rate was 40.2 percent in the group receiving unfractionated heparin and 53.4 percent in the group receiving reviparin twice daily.

In the Columbus Study,<sup>16</sup> reviparin was as effective as unfractionated heparin for the prevention of recurrent venous thromboembolism. The better efficacy of reviparin in the present study may be explained by the fact that in the patients in the Columbus Study there was a longer interval between the occurrence of symptoms and the initiation of treatment. Prolonged treatment with reviparin administered once daily without initial treatment with a vitamin K antagonist did not lead to an increased rate of recanalization of occluded veins, but it can be regarded as a safe and effective alternative to a regimen of reviparin administered twice daily with vitamin K antagonists for the early treatment of deep-vein thrombosis.

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**APPENDIX**

The following institutions and investigators participated in the study. Executive Committee: H.K. Breddin, V.V. Kakkar, V. Hach-Wunderle, and R.

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