

## TREATMENT OF VENOUS THROMBOSIS WITH INTRAVENOUS UNFRACTIONATED HEPARIN ADMINISTERED IN THE HOSPITAL AS COMPARED WITH SUBCUTANEOUS LOW-MOLECULAR-WEIGHT HEPARIN ADMINISTERED AT HOME

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**Abstract Background.** An intravenous course of standard (unfractionated) heparin with the dose adjusted to prolong the activated partial-thromboplastin time to a desired length is the standard initial in-hospital treatment for patients with deep-vein thrombosis, but fixed-dose subcutaneous low-molecular-weight heparin appears to be as effective and safe. Because the latter treatment can be given on an outpatient basis, we compared the two treatments in symptomatic outpatients with proximal-vein thrombosis but no signs of pulmonary embolism.

**Methods.** We randomly assigned patients to adjusted-dose intravenous standard heparin administered in the hospital (198 patients) or fixed-dose subcutaneous low-molecular-weight heparin administered at home, when feasible (202 patients). We compared the treatments with respect to recurrent venous thromboembolism, major bleeding, quality of life, and costs.

**Results.** Seventeen of the 198 patients who received standard heparin (8.6 percent) and 14 of the 202 patients who received low-molecular-weight heparin (6.9

percent) had recurrent thromboembolism (difference, 1.7 percentage points; 95 percent confidence interval, -3.6 to 6.9). Major bleeding occurred in four patients assigned to standard heparin (2.0 percent) and one patient assigned to low-molecular-weight heparin (0.5 percent; difference, 1.5 percentage points; 95 percent confidence interval, -0.7 to 2.7). Quality of life improved in both groups. Physical activity and social functioning were better in the patients assigned to low-molecular-weight heparin. Among the patients in that group, 36 percent were never admitted to the hospital at all, and 40 percent were discharged early. This treatment was associated with a mean reduction in hospital days of 67 percent, ranging from 29 percent to 86 percent in the various study centers.

**Conclusions.** In patients with proximal-vein thrombosis, treatment with low-molecular-weight heparin at home is feasible, effective, and safe. (N Engl J Med 1996;334:682-7.)

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**A**NTICOAGULANT treatment for deep-vein thrombosis aims to prevent pulmonary embolism and recurrent thrombosis and also to avoid excessive bleeding.<sup>1</sup> In addition, both the effect of therapy on the patients' well-being and the cost of therapy are factors to be weighed in determining the optimal treatment. It is current practice to treat acute venous thrombosis with intravenous standard (unfractionated) heparin for at least five days in a dose adjusted to lengthen the activated partial-thromboplastin time into a desired range.<sup>2-5</sup> Oral anticoagulant therapy is started concomitantly and continued for at least three months.<sup>6</sup> This approach is effective, but it suffers from the limitation that patients need to be admitted to the hospital, where intravenous infusion limits their mobility and they are exposed to the risks of hospital-acquired infections.<sup>2,3,7</sup>

The depolymerization of heparin yields low-molecu-

lar-weight heparins that have advantages over the parent compound, including better bioavailability, a longer half-life, and more predictable anticoagulant activity.<sup>8,9</sup> Therefore, they can be given subcutaneously, without laboratory monitoring, in a dose determined by the patient's body weight alone. Recent evidence suggests that fixed doses of subcutaneous low-molecular-weight heparin are as effective as adjusted doses of intravenous standard heparin and probably safer for the treatment of patients with thrombosis in the hospital.<sup>10-14</sup>

Outpatient therapy may be desirable for patients with deep-vein thrombosis, and the simplicity of treatment with low-molecular-weight heparin makes it attractive for home use. There is a reluctance to use it in this way, however, because of concern that efficacy may be compromised and that patients will become more apprehensive when treated away from a source of direct care. We therefore conducted a randomized trial in which patients with acute symptomatic proximal-vein thrombosis and no clinical evidence of pulmonary embolism were treated with either intravenous standard heparin given in the hospital or subcutaneous low-molecular-weight heparin in a more flexible strategy. Patients in the latter group who were willing and able to be treated at home were either not admitted to the hospital or discharged early. We sought to demonstrate clinical equivalence between the treatments in efficacy and safety, to confirm through quality-of-life assessments that home treatment had no adverse effects on patients'

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\*The study investigators are listed in the Appendix.

well-being, and to evaluate the use of resources associated with our policy of limited hospitalization among the patients assigned to therapy with low-molecular-weight heparin.

## METHODS

### Study Design

In an unblinded trial conducted in Europe, Australia, and New Zealand, we compared adjusted-dose intravenous standard heparin given in the hospital with fixed-dose subcutaneous low-molecular-weight heparin given at home when appropriate. The study protocol was approved by the institutional review boards at all the participating institutions.

### Patients

Consecutive outpatients with acute symptomatic proximal deep-vein thrombosis (i.e., thrombosis in the popliteal vein or a more proximal vein) documented by venography or ultrasonography were eligible.<sup>15</sup> A patient's ability to be treated at home was not considered in the assessment of eligibility. Patients were excluded from the study if they met one or more of the following criteria: venous thromboembolism within the preceding 2 years; suspected pulmonary embolism at presentation; previous treatment with heparin for more than 24 hours; geographic inaccessibility; a life expectancy of less than 6 months; overt post-thrombotic syndrome; age of less than 18 years; or pregnancy.

After the patients gave informed consent, randomization (stratified according to center) was achieved by means of a central 24-hour telephone service.

### Treatment Regimens

Patients randomly assigned to standard heparin were admitted to the hospital and received heparin sodium in an intravenous loading dose of 5000 IU (Laboratoires Choay, Paris), followed by a continuous infusion of 1250 IU per hour. The dose was adjusted so that the activated partial-thromboplastin time would be from 1.5 to 2 times the mean value in normal subjects, as measured with a sensitive reagent (corresponding to 0.35 to 0.6 International Factor Xa Inhibitory Unit per liter).<sup>1</sup> The tests were performed six hours after the start of treatment or if a subtherapeutic activated partial-thromboplastin time had been measured, and otherwise daily.

The patients randomly assigned to low-molecular-weight heparin received twice-daily injections of nadroparin-Ca (Fraxiparine, Sanofi Winthrop, Paris) with prefilled syringes, in doses adjusted for the patient's weight. Patients weighing less than 50 kg received a total daily dose of 8200 International Factor Xa Inhibitory Units per liter; those weighing between 50 and 70 kg, 12,300 International Factor Xa Inhibitory Units per liter; and those weighing over 70 kg, 18,400 International Factor Xa Inhibitory Units per liter. There was no laboratory monitoring. Each patient was instructed by a nurse in the method of self-injection. If self-administration was impossible, the injections were given by a relative or a nurse. As soon as appropriate, patients were allowed to be treated at home.

In each patient, oral anticoagulant treatment was initiated on the first day and continued for a total of three months, unless the persistence of risk factors required its continuation beyond that period.<sup>2,6</sup> The dose was adjusted to achieve an international normalized ratio of 2.0 to 3.0.<sup>2,4</sup> The intensity of anticoagulation in the first three months was expressed as the percentage of time during which a patient had a specific international normalized ratio (<2.0, 2.0 to 3.0, or >3.0), with this period calculated by linear interpolation.<sup>16</sup> Treatment with either standard heparin or low-molecular-weight heparin was continued until the international normalized ratio was 2.0 or above in two measurements 24 hours apart after at least five days of initial treatment.

### Surveillance and Follow-up

All the patients were contacted daily during the initial treatment and at 4, 12, and 24 weeks. A checklist was used to elicit data on signs and symptoms of recurrent venous thromboembolism or bleeding. In

cases of suspected recurrent thrombosis (i.e., when there was increased pain or swelling in the leg), venography or ultrasonography was performed. Patients with suspected pulmonary embolism (i.e., who had dyspnea or chest pain) underwent ventilation-perfusion scanning or angiography.<sup>17</sup> During the initial treatment, platelet counts were obtained twice weekly. Thrombocytopenia was defined as present when the count was below 100,000 platelets per cubic millimeter.

### Assessments of Clinical Outcome

The primary outcome event studied was symptomatic recurrent venous thromboembolism. The criterion for this event was one of the following: a new defect of intraluminal filling detected in more than one projection on venography; a lack of compressibility at a new site or a definite increase in thrombus size as detected on compression ultrasonography;<sup>2,10,15,18</sup> a segmental or larger perfusion defect during normal ventilation, detected on ventilation-perfusion scanning; and a constant defect of intraluminal filling or the sudden blockage of a vessel as detected on pulmonary angiography.<sup>17</sup>

The secondary outcome event, major bleeding, was defined as overt hemorrhage associated with a decrease in the hemoglobin level of at least 2.0 g per deciliter or that necessitated a transfusion of at least 2 units of red cells, caused retroperitoneal or intracranial bleeding, or led to bleeding that warranted the permanent cessation of treatment.

Documentation of all potential outcome events, including deaths, was submitted to an independent adjudication committee whose members were unaware of the treatment assignments.

### Biometric Analysis

The primary analysis concerned the incidence of recurrent venous thromboembolism during the first six months, and the secondary analysis dealt with the incidence of major bleeding during the first three months. These analyses were performed on an intention-to-treat basis. The results are reported as differences in incidence and 95 percent confidence intervals.<sup>19</sup>

On the basis of our earlier observation of a 13.3 percent reduction in the incidence of recurrent thromboembolism associated with the use of intravenous standard heparin as compared with placebo,<sup>2</sup> and in view of the possible advantages of low-molecular-weight heparin, we reasoned that if the lower confidence limit indicated that low-molecular-weight heparin was inferior by less than 5 percent, clinical equivalence between the treatments would be demonstrated. Assuming a 5 to 6 percent incidence of recurrent thromboembolism in the low-molecular-weight-heparin group and a 7 to 8 percent incidence in the standard-heparin group,<sup>2,5,10-14</sup> a sample containing 200 patients in each group would be needed (one-sided alpha, 0.05; beta, 0.20).

### Quality of Life

We assessed quality of life from an overall, multidimensional perspective and also used a generic, disease-specific approach. The Medical Outcome Study Short Form-20 was used to assess each patient's mental health, perception of health, degree of pain, physical activity, role fulfillment, and social functioning. This instrument was developed as a generic measure<sup>20</sup> and validated in English and Dutch.<sup>21</sup> Since no disease-specific instrument was available for use in the assessment of patients with thrombosis, we adapted the Rotterdam Symptom Checklist,<sup>22</sup> adding four items for symptoms specific to thrombosis of the leg: swelling, a heavy feeling, pain in the calf, and pain in the thigh. We used a visual-analogue scale<sup>23</sup> to assess the effort needed to cope with illness and the regimen of treatment, as well as to assess overall quality of life. The patients answered each question with reference to the previous week.

The patients completed the first questionnaire before randomization. Subsequently, short-term changes (those that occurred after initial treatment was stopped) and long-term changes (those observed 12 and 24 weeks after randomization) were evaluated. A nurse was available to help patients complete the questionnaires if necessary, but the nurse was instructed not to influence the patients' responses.

On the basis of an analysis of principal components, we created

subscales for the modified Rotterdam Symptom Checklist. The reliability of the multi-item scales was estimated by computing their internal consistency at base line and at the second measurement. Scores on single- and multi-item scales were transformed into scores on a scale from 0 to 100.

The main effects of treatment and time were established by multivariate repeated-measures analysis of variance. If we found interactions, we explored the differences between groups by univariate analysis (using Student's *t*-test). We analyzed the data to determine whether age and sex were related to quality of life independently or in interaction with treatment.

### Use of Resources

Because it is difficult to compare medical costs among countries,<sup>24</sup> we compared the two treatment strategies in terms of use of resources. The duration of treatment, the length of the hospital stay, the number of outpatient visits, and the frequency of telephone calls for medical information were all obtained from the case-record forms. For a random sample of 78 patients, additional information was collected on professional care provided to patients or their relatives at home. The costs of conducting the study were excluded from the evaluation.

## RESULTS

### Patients

Of 692 eligible patients, 216 (31 percent) were excluded, for the following reasons: recent venous thromboembolism (38 patients), suspected pulmonary embolism (33), previous use of anticoagulant drugs for more than 24 hours (27), geographic inaccessibility rendering follow-up impracticable (33), short life expectancy (14), post-thrombotic syndrome (8), other reasons (16), or some combination of the above (47). Seventy-six of the remaining 476 patients (16 percent) did not consent to participate. Thus, 400 patients were randomized, 198 to receive standard heparin and 202 to receive low-molecular-weight heparin. Shortly after randomization, two patients (one in each group) withdrew their con-

Table 1. Clinical Characteristics of the Study Patients According to Treatment Group.

CHARACTERISTIC	STANDARD HEPARIN (N = 198)	LOW-MOLECULAR- WEIGHT HEPARIN (N = 202)
Mean ( $\pm$ SD) age (yr)	62 $\pm$ 16	59 $\pm$ 17
Weight (kg)		
Median	74	75
Range	44–115	43–145
	<i>no. of patients (%)</i>	
Male sex	96 (48)	107 (53)
Body-mass index >27*	75 (38)	67 (33)
Delay of <14 days in seeing physician	155 (78)	152 (75)
Deep-vein thrombosis of the femoral vein or a more proximal site	134 (68)	140 (69)
Risk factors		
Previous venous thromboembolism	38 (19)	40 (20)
Known cancer	36 (18)	34 (17)
Surgery in past 3 mo	31 (16)	24 (12)
Trauma in past 3 mo	22 (11)	24 (12)
Immobilization	49 (25)	50 (25)
$\geq$ 2 of these	42 (21)	41 (20)

\*Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

Table 2. Heparin Therapy Provided to the Study Patients, According to Treatment Group.

GROUP AND VARIABLE	VALUE
<b>Standard heparin (n = 198)</b>	
Mean ( $\pm$ SD) days of initial treatment	6.1 $\pm$ 1.8
Mean dose of standard heparin — IU	
Day 1	29.104
Day 2	27.774
Activated partial-thromboplastin time prolonged as desired — % of patients*	
Within 24 hr	81
Within 48 hr	94
<b>Low-molecular-weight heparin (n = 202)</b>	
Mean ( $\pm$ SD) days of initial treatment	6.5 $\pm$ 2.2
Hospitalization status during treatment — no. of patients (%)	
Not admitted	72 (36)
Discharged during initial treatment	
After <48 hr	44 (22)
After $\geq$ 48 hr	36 (18)
Treated entirely in the hospital	50 (25)

\*We sought to lengthen the activated partial-thromboplastin time to more than 1.5 times the mean value obtained in normal subjects with a sensitive reagent.

sent. They were included in the follow-up, and they allowed their data to be used. The two treatment groups had similar characteristics at entry into the study (Table 1).

### Treatment and Follow-up

Data on the duration and adequacy of the initial treatment and the hospitalization of the study patients are shown in Table 2. The initial treatment lasted a mean of six days in each group. The results of treatment with standard heparin were adequate in 94 percent of patients at 48 hours. Among the recipients of low-molecular-weight heparin, 36 percent were never admitted to the hospital, and another 40 percent were discharged before the initial treatment had ended. Four patients, two in each group, were lost to follow-up after 12 weeks. The intensity and duration of oral anticoagulant therapy in the two groups are shown in Table 3. Thrombocytopenia from which the patient recovered spontaneously without clinical symptoms was observed in five patients assigned to standard heparin and three patients assigned to low-molecular-weight heparin.

### Recurrent Venous Thromboembolism

Symptomatic recurrent venous thromboembolism was documented in 17 patients assigned to standard heparin (8.6 percent) and 14 patients assigned to low-molecular-weight heparin (6.9 percent) (absolute difference in favor of low-molecular-weight heparin, 1.7 percentage points; 95 percent confidence interval,  $-3.6$  to  $6.9$ ) (Table 4). Of the 17 events in the standard-heparin group, 12 involved recurrent thrombosis and 5 involved pulmonary embolism (from which one patient died, 120 days after randomization). Of the 14 events in the low-molecular-weight-heparin group, 10 involved recurrent thrombosis and 4 involved pulmonary embolism

**Table 3. Intensity and Duration of Oral Anticoagulant Therapy in the Study Patients According to Treatment Group.**

VARIABLE	STANDARD HEPARIN (N = 198)	LOW-MOLECULAR-WEIGHT HEPARIN (N = 202)
	% of time*	
International normalized ratio		
<2.0	18	16
2.0 to 3.0	56	62
>3.0	26	22
	% of patients	
Therapy continuing after 3 mo	39	36

\*Values indicate the percentage of time in the first three months of treatment during which the international normalized ratio was in the category shown.

(from which two patients died, 113 and 164 days after randomization).

**Major Bleeding**

Major bleeding occurred in four patients assigned to standard heparin (2.0 percent) and one patient assigned to low-molecular-weight heparin (0.5 percent), an absolute difference of 1.5 percentage points in favor of low-molecular-weight heparin (95 percent confidence interval, -0.7 to 2.7) (Table 4). The hemorrhages in the standard-heparin group consisted of retroperitoneal bleeding on the first day, hematuria on the second day, and upper gastrointestinal and intracranial bleeding 18 and 28 days after randomization. The patients who had retroperitoneal and intracranial bleeding died. In the low-molecular-weight-heparin group, the episode of major bleeding was a nonfatal hemorrhage (lower gastrointestinal bleeding) that occurred six days after randomization. Overall, 15 episodes of minor bleeding (including epistaxis, hematuria, and skin hematomas) were reported in the standard-heparin group, as compared with 27 in the low-molecular-weight-heparin group.

**Mortality**

Sixteen recipients of standard heparin (8.1 percent) and 14 recipients of low-molecular-weight heparin (6.9 percent) died during the six-month study period (Table 4). No patient died during the initial treatment. The causes of death included cancer (16 patients, 8 in each group), pulmonary embolism (3 patients), bleeding (4 patients, 2 of whom died after the first three months), cardiovascular disease (6 patients), and septic shock (1 patient).

**Quality of Life**

Quality-of-life questionnaires were completed by 94.5 percent of patients at entry into the study, by 92.3 percent at the end of the initial treatment, by 89.1 percent after 12 weeks, and by 82.3 percent after 24 weeks. The proportions of missing data in the questionnaires were

1.4, 1.5, 2.1, and 2.5 percent at the respective measurement points. The principal-component analysis yielded three relevant factors: psychological distress, fatigue, and symptoms of thrombosis. The reliability of the multi-item scales ranged from 0.76 to 0.92. No differences between treatment groups were found at base line. Time had an effect on quality of life, with improvement in all indicators (P<0.001), the most important of which are shown in Figure 1. The changes over time were similar in both groups, except that the patients receiving low-molecular-weight heparin had better scores for physical activity (P=0.002) and social functioning (P<0.001) at the end of the initial treatment (Fig. 1). As would be expected, younger patients and men had better scores for quality of life than older patients and women (P=0.008 for both), but we found no interaction between age and sex and the effects of treatment or time.

**Use of Resources**

Of the patients assigned to low-molecular-weight heparin, 75 percent either were not admitted to the hospital initially or were discharged early (Table 2). Five of these patients were admitted to the hospital during the initial treatment (because of thromboembolic events in two and bleeding, cancer, and inadequate housing in one each). Among patients with no suspected event, the average hospital stay was 2.7 days in the low-molecular-weight-heparin group, as compared with 8.1 days in the standard-heparin group, a reduction of 67 percent in the duration of hospitalization. This reduction during the initial treatment ranged from 29 percent to 86 percent at the various participating centers. The reduction was accompanied by an average of 2.0 outpatient visits and 2.2 telephone calls per patient. Fifteen

**Table 4. Recurrent Venous Thromboembolism, Major Bleeding, and Death in the Study Patients According to Treatment Group.\***

EVENT AND TIME OF OCCURRENCE	STANDARD HEPARIN (N = 198)	LOW-MOLECULAR-WEIGHT HEPARIN (N = 202)
Recurrent venous thromboembolism — no. of patients (%)		
Days 0-14	5	4
Days 15-84	5	4
Day 85 to end of follow-up	7	6
All	17 (8.6)	14 (6.9)
	Difference, 1.7 percentage points (95% CI, -3.6 to 6.9)	
Major bleeding — no. of patients (%)		
Days 0-14	2	1
Days 15-84	2	0
All	4 (2.0)	1 (0.5)
	Difference, 1.5 percentage points (95% CI, -0.7 to 2.7)	
Death — no. of patients (%)		
Days 0-14	0	0
Days 15-84	7	4
Day 85 to end of follow-up	9	10
All	16 (8.1)	14 (6.9)
	Difference, 1.2 percentage points (95% CI, -4.0 to 6.3)	

\*CI denotes confidence interval.

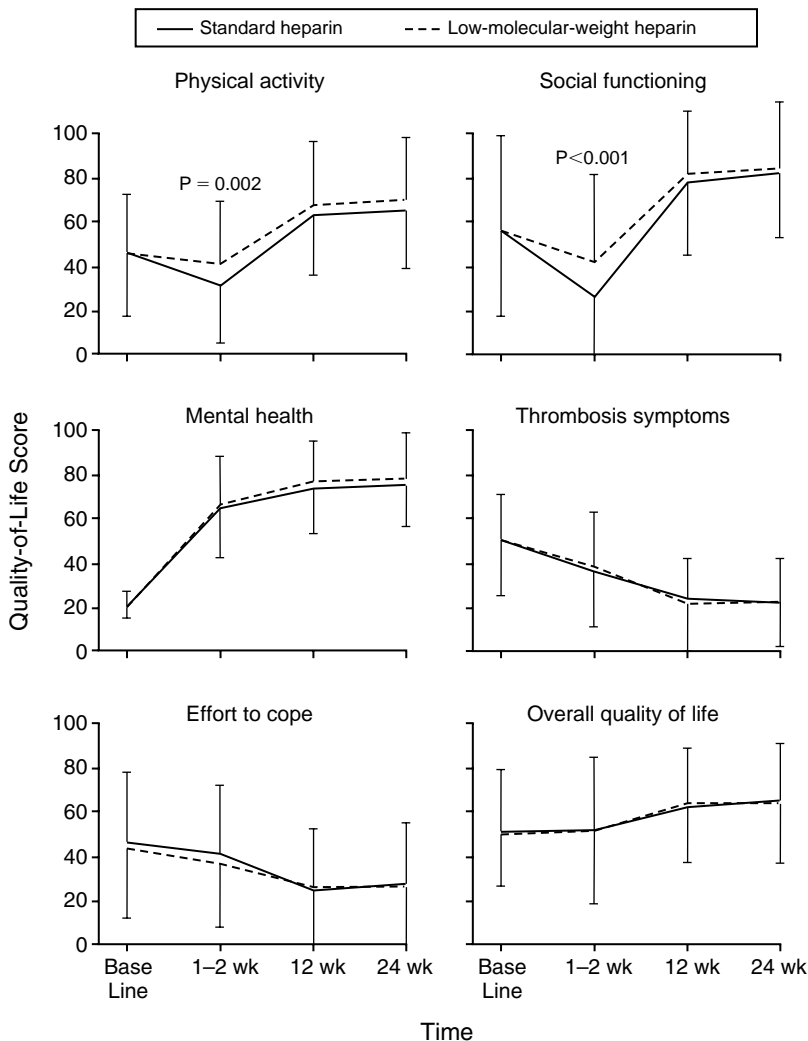


Figure 1. Mean ( $\pm$ SD) Changes over Time in Various Indicators of Quality of Life as Reported by the Patients in the Two Treatment Groups.

At each measurement point, the patients completed the Medical Outcome Study Short Form-20<sup>20,21</sup> and a modified version of the Rotterdam Symptom Checklist,<sup>22</sup> as described in the Methods section. Scores on single- and multi-item scales were transformed into scores on a scale from 0 to 100, with higher scores indicating better quality of life. P values shown are for the comparisons between groups at the times indicated.

percent of the patients treated at home received professional help in administering their injections.

## DISCUSSION

Recent clinical studies suggest that low-molecular-weight heparins given subcutaneously in fixed doses can replace standard (unfractionated) intravenous heparin in the treatment of deep-vein thrombosis.<sup>10-14</sup> The simplicity of this therapy contrasts with the complexity of treatment using standard heparin and raises the important practical question of whether low-molecular-weight heparins can be used to treat patients outside the hospital.

Our trial was designed to evaluate this possibility, and it demonstrates that low-molecular-weight heparin is at

least as effective and safe as standard heparin but permits approximately 75 percent of patients to be treated as outpatients or discharged early from the hospital. Rates of recurrent thromboembolism and major bleeding were both low and similar in the two treatment groups.

The concern that patients might react negatively to being treated at home for this serious condition was not supported by the results of the quality-of-life assessment. The indicators used, including emotional well-being and the amount of effort needed to cope with the condition, improved similarly over time in both groups. However, treatment with low-molecular-weight heparin was associated with less impairment of physical activity and social functioning.

As compared with standard-heparin therapy, our flexible strategy of treatment with low-molecular-weight heparin substantially reduced the average hospital stay. The increased need for outpatient and home health services did not offset this decreased use of resources.

Because this was an unblinded trial, care was taken to minimize the potential for bias. We therefore included consecutive patients, relied on central randomization by telephone, and ensured that follow-up was complete and standardized in nearly all patients. Furthermore, all suspected outcome events were adjudicated by an independent and blinded committee using predetermined criteria.

Another concern relates to the generalizability of the study. The demographic characteristics of our patients, as well as the extent of throm-

bolism, the frequency of coexisting conditions, the prevalence of predisposing risk factors, and the rate of outcome events, compare well with those in earlier studies.<sup>2,3,5,10,11</sup> This similarity, together with the low proportion of patients (16 percent) who met the criteria for study entry but refused to give consent for participation, supports the hypothesis that our findings can be generalized to all outpatients with symptomatic proximal deep-vein thrombosis. Because we excluded patients with symptomatic pulmonary embolism, our findings do not apply to those patients.

Quality of life was measured with the Medical Outcome Study Short Form-20, a modified version of the Rotterdam Symptom Checklist, and two visual-analogue scales. The Short Form was selected because, although it

was originally developed for patients with chronic conditions, it proved to be sensitive in a study of patients receiving anticoagulant therapy.<sup>25</sup> The version used in the present study, as well as other parts of the questionnaire, has good reliability and is sensitive to changes over time. We are therefore confident that the quality-of-life findings adequately reflect the status of the patients.

Deep-vein thrombosis is a major clinical problem in Western countries, with an estimated annual incidence of 1 per 1000 inhabitants.<sup>26</sup> This rate implies that each year approximately 250,000 Americans need to be hospitalized for 5 to 10 days of intravenous heparin therapy. Therefore, our results have broad implications, especially since this trial was probably conservative in the proportion of patients who were treated at home, given the novelty of this approach.

The change in emphasis from in-hospital treatment to community care is consistent with worldwide trends. Three potential hazards must be recognized, however. Because the clinical diagnosis is unreliable, the presence of the disease should be confirmed objectively in every patient to avoid unnecessary treatment.<sup>15,26</sup> Second, an adequate assessment of risk factors to explain the possible cause of thrombosis must be made.<sup>27,28</sup> Finally, care outside the hospital increases pressure on community facilities to provide proper anticoagulant therapy, and they need to be prepared for this task.

We conclude that a flexible strategy using low-molecular-weight heparin to treat patients with proximal-vein thrombosis, one tailored to their clinical and personal needs that includes home treatment for suitable patients, is effective and safe, has no measurable adverse effects on physical or mental well-being, and reduces costs.

#### APPENDIX

The following investigators also participated in this study: **Study Centers:** Academic Medical Center, Amsterdam — J.W. ten Cate, H. Jagt, and Y. Jenner; Istituto di Semeiotica Medica, Padua, Italy — S. Villalta, L. Scarano, and B. Girolami; Medicina Interna e Oncologica Medica, Pavia, Italy — M. Barone, C. Beltrametti, S. Siragusa, and L. Vicentini; Auckland Hospital, Auckland, New Zealand — A. Bennett; Slotervaart Hospital, Amsterdam — M. de Rijk and O. Termede; Academic Hospital Groningen, Groningen, the Netherlands — G. Que; Martini Hospital, Groningen — J. van Ingen and L. Wijnja; Flinders Medical Center, Adelaide, Australia — J. Stevens and W. Mills; Hôpital Clamart, Paris — F. Parent; and Prince of Wales Hospital, Sydney, Australia — S. Pritchard and B. Choong. **Central Data Management Office:** Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam — A. van Barneveld, Y. Graafsma, R. Hettiarachchi, J. Lok, and J.G.P. Tijssen; and Department of Medical Psychology, Academic Medical Center, Amsterdam — W. Wijker. **Adjudication Committee:** A.W.A. Lensing, M.V. Huisman, and H. Heyboer (Amsterdam). **Safety Committee:** D. Bergqvist (Malmö, Sweden) and D.A. Wood (London). **Writing Committee:** N.H. Chapman. **Sanofi Winthrop:** M. Midavaine (France), N.H. Chapman and L.B. Coy (Australia), J. Hoek (the Netherlands), and P. Montanari (Italy).

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**CORRECTION**

**Treatment of Venous Thrombosis with Intravenous Unfractionated Heparin Administered in the Hospital as Compared with Subcutaneous Low-Molecular-Weight Heparin Administered at Home**

Treatment of Venous Thrombosis with Intravenous Unfractionated Heparin Administered in the Hospital as Compared with Subcutaneous Low-Molecular-Weight Heparin Administered at Home . On page 683, in the left-hand column, in line 17 under the heading "Treatment Regimens," the International Factor Xa Inhibitory Units per liter for patients weighing over 70 kg should have been 16,400, not 18,400, as printed.