

Low Molecular Weight Heparin versus Acenocoumarol in the Secondary Prophylaxis of Deep Vein Thrombosis

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Summary

The aim of this study was to determine the efficacy and safety of subcutaneous weight-adjusted dose low molecular weight heparin (LMWH) compared with oral anticoagulant (OA) in the prevention of recurrent venous thromboembolism. In a prospective multicenter trial, 202 patients with symptomatic proximal deep vein thrombosis (DVT) were included. As soon as the diagnosis of DVT was confirmed by phlebography, 101 were randomly assigned to receive LMWH (nadroparin) for secondary prophylaxis and 101 to receive OA (acenocoumarol). Patients in both groups were initially treated with nadroparin in a dose of 85 anti-Xa IU/kg s.c. every 12 h. Secondary prophylaxis with either nadroparin, 85 anti-Xa IU/kg s.c. once daily, or acenocoumarol was continued for at least 3 months. Three patients in the LMWH group and 6 in the OA group were excluded from analysis for various reasons. During the one-year combined secondary prophylaxis and surveillance period, 7 of the 98 evaluable patients (7.1%) in the LMWH group and 9 of the 95 evaluable patients (9.5%) in the OA group had a documented recurrence of venous thromboembolism (Fisher's exact test, $p = 0.61$). Of these, 2 patients who received LMWH and 7 patients on acenocoumarol had recurrences in the 3-month period of secondary prophylaxis. Four patients (4.1%) in the LMWH group developed bleeding complications during this study period, as compared with 7 (7.4%) in the OA group (Fisher's exact test, $p = 0.37$). There were two major bleedings, one in the LMWH group and one in the OA group. Eleven patients died, 5 (5.1%) in the LMWH group and 6 (6.3%) in the OA group. It is concluded that nadroparin in a dose of 85 anti-Xa IU/kg s.c. once daily provides an effective and safe alternative to oral anticoagulants in the secondary prophylaxis of DVT.

Introduction

The standard treatment in patients with deep vein thrombosis (DVT) consists of the intravenous infusion of unfractionated heparin (UFH) for 5 to 10 days (initial therapy) followed by the administration of an

oral anticoagulant for at least 3 months (secondary prophylaxis). Although long-term anticoagulation with coumarin drugs, the most popular of which are warfarin and acenocoumarol, has been repeatedly demonstrated effective in the prevention of recurrent venous thromboembolism, it suffers from a number of limitations. This treatment requires strict laboratory control and consequent adjustments of the drug dosage and carries a substantial risk of bleeding complications (1). Furthermore, it is unacceptable for pregnant women because coumarin drugs cross the placenta and confer a risk of characteristic embryopathy, if prescribed in the first trimester, and central nervous system abnormalities at every stage of pregnancy (2).

Recently, several randomized studies have shown that low molecular weight heparins (LMWHs) are safe and effective in preventing venous thromboembolism (3, 4), and at least as safe and effective as UFH in the initial treatment of acute deep vein thrombosis (5-12). In two recent studies they have also been administered successfully in patients with pulmonary embolism (13, 14). LMWHs have better bioavailability when administered subcutaneously, a longer plasma half-life, and more predictable anticoagulant response than UFH (15). These properties allow LMWHs to be administered subcutaneously either once or twice daily in doses adjusted only to the patient's weight, without laboratory monitoring. Their use may be associated with lower risk of heparin-induced osteoporosis compared to UFH (16, 17). It is still an open question whether LMWH can be used as an alternative to oral anticoagulants in the prevention of recurrences after DVT. This study was designed to determine the efficacy and safety of subcutaneous weight-adjusted dose LMWH compared with acenocoumarol in the secondary prophylaxis of DVT.

Patients and Methods

Selection of patients. Patients 18 years of age or older with phlebographically proven proximal DVT (thrombosis involving the popliteal vein or a more proximal vein) and duration of symptoms not longer than 3 weeks were considered for the study. Patients were excluded from the study if they had any of the following: contraindication to anticoagulant therapy, pregnancy, phlegmasia coerulea dolens, documented hereditary thrombophilia, antiphospholipid antibodies, thrombolytic therapy or operation scheduled, recent surgery (<8 days), intervention in the central nervous system within the last 4 weeks, concurrent symptomatic pulmonary embolism, history of venous thromboembolism in the last two years, treatment with UFH, LMWH or oral anticoagulants more than 72 h prior to enrollment, malignancy or aneurysm known to be the local cause

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of venous occlusion, obstruction of the vena cava by a filter, known allergy to iodine, life expectancy of less than 6 months, treatment with platelet function inhibitors that could not be discontinued, an inability for follow-up visits to the clinic. The study protocol was reviewed and approved by the ethics committees of the participating centers.

Study design. This was a prospective, open, randomized, two-armed clinical trial conducted in 11 centers in Poland. The recruitment period was 19 months, from April 1995 to November 1996. As soon as diagnosis of proximal DVT was confirmed by phlebography, informed consent was obtained and, prior to the initial treatment, eligible patients were randomly allocated (through a system of sealed envelopes) to receive for the secondary prophylaxis either LMWH (nadroparin) or oral anticoagulant (acenocoumarol).

Treatment regimens. The patients were hospitalized for approximately 2 weeks and then treated at home under supervision of the treatment center. The initial therapy was similar for both groups: the patients received nadroparin (Fraxiparine, Sanofi Winthrop, Paris) in a fixed dose of 85 anti-Xa IU (225 anti-Xa Institute Choay units) per kilogram of body weight s.c. twice daily. The medication was supplied in prefilled syringes each containing 5700 anti-Xa IU in 0.6 ml or 9500 anti-Xa IU in 1.0 ml (15,000 or 25,000 anti-Xa Institute Choay units). There was no laboratory monitoring. Whenever possible, patients were allowed to walk on the third day of initial therapy, wearing elastic support.

In the LMWH group, high-dose nadroparin was administered for 10 days, and from day 11 onwards the patients still received subcutaneous injections of nadroparin in a fixed dose of 85 anti-Xa IU per kilogram of body weight, but only once daily. Upon discharge from the hospital the patients received a three to four-week supply of nadroparin in prefilled syringes. Each patient was instructed by a study nurse in the method of self-injection and was informed about the excess amount of LMWH to be removed before the injection. If self-administration was impossible, the injections were given by a relative or a visiting nurse.

In the OA group, high-dose nadroparin was administered for 10 days, provided the INR on day 11 was 2.0 or more, or 1 to 2 days longer, in the INR was below 2.0. The treatment with acenocoumarol (Acenocoumarol, Polfa-Warsaw, 4 mg tablets) was initiated on day 7 of the initial therapy, i.e. at least four days before subcutaneous LMWH was discontinued. The doses were as follows: 1st day – 6 mg, 2nd day – 4 mg, from the 3rd day onwards – adjusted to maintain the INR between 2.0 and 3.0.

Secondary prophylaxis with either LMWH or oral anticoagulant was continued for at least 3 months. During the initial treatment, hemoglobin and hematocrit measurements, blood platelet counting and urine analysis were carried out every second day. In patients assigned to OA, prothrombin time was measured at least every second day during hospitalization, starting from the third day of the drug administration, and then at least every third week. The quality of anticoagulation in each patient was estimated as good, if at least 4 of the 6 INR values (on day 11-12, before discharge and during follow-up visits) were ≥ 2.0 , or poor, if 3 or more INR values were < 2.0 .

Table 1 Reasons for exclusion of patients (n = 9) from analysis. Figures are numbers of patients

	Patients assigned to LMWH	Patients assigned to OA
Exclusion criterion overlooked (vein compressed by arterial aneurysm) ^a		2
Consent withdrawal (D10, D15 and D22)		3
Sudden death during initial treatment (D10)	1	
Symptomatic pulmonary embolus during initial treatment (D3) and vena cava filter insertion (D14)	1	
Initial treatment changed:		
- thrombectomy (D3)		1
- treatment with unfractionated heparin (D2-D10)	1	

^aAneurysms of the iliac and popliteal arteries; patients underwent reconstructive vascular surgery on D11 and D49, respectively.

Assessment of venous thromboembolism. Ascending phlebography was performed using non-ionic contrast medium (Ultravist 300, Schering) in all the patients before entry into the trial and repeated during follow-up only in those with clinically suspected recurrent DVT. The criteria for DVT were a constant intraluminal filling defect confirmed in at least two projections or nonvisualization of a vein or a venous segment, despite adequate technique. Recurrent thrombosis was diagnosed if there was a new constant intraluminal filling defect compared to the baseline phlebography (18, 19).

Chest X-ray and perfusion or ventilation-perfusion lung scans were performed in all patients within 72 h of enrollment and their results were interpreted according to standard procedures (20). A new perfusion or ventilation-perfusion lung scan was performed only in patients with clinically suspected pulmonary embolism. If the lung scan was inconclusive, pulmonary angiography was done. A recurrence was defined as a new segmental or greater perfusion defect or a positive pulmonary angiogram (an intraluminal defect or a sudden cutoff in the area where the initial perfusion lung scan showed normal perfusion).

Compliance. Compliance in patients randomized to LMWH was monitored by checking injection sites and syringe counts at follow-up visits. Compliance in patients randomized to OA was monitored through the prothrombin time determination.

Follow-up. After discharge, the patients were seen routinely by the physician at the treatment center at fixed intervals and were instructed to report at once if symptoms or signs suggestive of DVT, pulmonary embolism or bleeding developed. At each visit (3, 6, 9 and 12 weeks and then 6, 9 and 12 months after the end of the initial treatment) a history was taken, physical examination performed and blood samples collected for the complete blood count. In patients on acenocoumarol the prothrombin time was also determined.

Outcome events. The principal outcome events studied in this trial were symptomatic recurrent venous thromboembolism within one year after the initial therapy (i.e. during the 3-month secondary prophylaxis and 9-month surveillance period) confirmed by objective testing, and bleeding during the 3-month secondary prophylaxis. Bleeding was defined as major if it was overt and associated with a fall in the hemoglobin level of 2.0 g/dl or more or with a need for the transfusion of 2 or more units of packed red cells, or if it was retroperitoneal or intracranial. Bleeding was defined as minor if it was clinically overt but did not meet the criteria for major bleeding. Other outcomes were the occurrence of thrombocytopenia and total mortality. Thrombocytopenia was defined as present if the platelet count fell below $100 \times 10^9/l$. Heparin-induced thrombocytopenia type II was defined as a marked reduction in the platelet count appearing five or more days after the start of heparin therapy plus a positive test for the presence of heparin-dependent antibodies (21).

Statistical analysis. The sample size calculation was based on the comparison of the two study groups with respect to the incidence of recurrent venous thromboembolism. Based on results of previous trials (1, 22, 23), the expected incidence of recurrences in the OA group was 15% during one year of follow-up. Under this assumption, 90 patients per group were required to ensure that a 2-fold increase in the incidence of recurrent venous thromboembolism in the LMWH group would be detected with an α error of 0.05 and β error of 0.2.

The results were compared by Fisher's exact test. A probability value less than 0.05 was considered significant.

Results

Study Patients

A total of 202 patients with phlebographically confirmed proximal DVT were entered into the trial and randomized to either LMWH group (n = 101) or OA group (n = 101). Of these, 9 patients were excluded from the analysis, 3 assigned to LMWH and 6 assigned to OA. Reasons for the exclusion are listed in Table 1. There was one sudden death of unknown cause (necropsy was not performed) and one symptomatic pulmonary embolism confirmed by scintigraphy in the LMWH group during the initial treatment. One patient of this group was shifted to unfractionated heparin on the 2nd day of initial treatment following the decision of a physician based on clinical signs suggestive of the

patient's unresponsiveness to LMWH. This was considered a protocol violation. Of the OA group, in 2 patients an exclusion criterion was overlooked prior to randomization and in 3 the secondary prophylaxis could not be controlled at the treatment center because of consent withdrawal. In one patient of this group with a floating thrombus in the iliac vein a surgical thrombectomy was performed on the 3rd day after randomization.

Thus, for the final analysis there were 98 evaluable patients in the LMWH group and 95 in the OA group. The treatment groups did not differ in basic features such as sex, age, weight and duration of symptoms (Table 2). Likewise, the incidence of various predisposing factors did not vary significantly between the two groups. The proportion of patients with malignant disease was approximately 6% in either group.

None of the patients refused to accept the LMWH treatment because of their dislike for subcutaneous injections. Sixty patients received nadroparin by self-injections, in 25 the injections were performed by a visiting nurse, and in 13 by a relative. Anticoagulation with acenocoumarol during the 3-month secondary prophylaxis was estimated as good in 79% of patients and poor in 21%.

Recurrent Venous Thromboembolism

During the one year follow-up (3-month secondary prophylaxis and 9-month surveillance period), 7 of the 98 patients (7.1%) in the LMWH group had a documented recurrence of venous thromboembolism, as compared with 9 of the 95 patients (9.5%) in the OA group (Fisher's exact test, $p = 0.61$). All recurrences of DVT, except one in the OA group, were in the same limb. There were 7 episodes of symptomatic pulmonary embolism, 2 in the LMWH group and 5 (one fatal) in the OA group (Table 3).

Two patients receiving LMWH and 7 on acenocoumarol developed recurrences during the 3-month secondary prophylaxis (Fisher's exact test, $p = 0.10$). In the subsequent 9-month surveillance period, there were 7 recurrences of venous thromboembolism; 5 in patients assigned to LMWH and 2 in patients assigned to OA (Fisher's exact test, $p = 0.45$). Within this period, 21 patients (22%) in the OA group had the acenocoumarol treatment prolonged to 6 months, 5 (5%) to 9 months and 15 (16%) to one year, following the advice of their treating physician. Treatment with nadroparin was prolonged to 4 or 5 months in 7 patients (7%), and to 9 months in 1 patient (1%) of the LMWH group. All new episodes diagnosed during the surveillance period, except one in the OA group, occurred in patients no longer treated with an anti-coagulant.

Complications Involving Bleeding

No hemorrhagic complications were observed during the 10-day initial treatment period. During the 3-month period of secondary prophylaxis, there were 4 bleeding events among the patients treated with LMWH and 7 among those on acenocoumarol (Fisher's exact test, $p = 0.37$). Of these, 2 involved major bleeding, one in the LMWH group and one in the OA group (Table 4). Both patients with major bleeding required hospitalization and transfusions of packed red cells. In neither case a predisposing disorder was found. The minor bleedings were hematuria, gingival and epistaxis which did not require hospital admission. During the surveillance period, one patient in the LMWH group developed gastrointestinal bleeding; the patient had metastatic cancer and died shortly after the event of the neoplastic disease progression.

None of the patients developed heparin-induced thrombocytopenia type II. Two patients in the LMWH group and 2 in the OA group had a

Table 2 Base-line characteristics of the study patients eligible for final analysis

Characteristic	LMWH group	OA group
Evaluable number	98	95
Sex (male:female)	45:53	49:46
Mean (\pm SD) age (yr)	56.6 \pm 16.2	57.8 \pm 14.6
Mean (\pm SD) weight (kg)	74.9 \pm 14.8	76.2 \pm 15.0
	no. of patients (%)	
Duration of symptoms		
\leq 5 days	51 (52)	48 (50)
6-10 days	32 (33)	33 (35)
11-21 days	15 (15)	14 (15)
Predisposing factors		
Previous venous thromboembolism	14 (14)	17 (18)
Malignancy	6 (6)	6 (6)
Recent surgery or trauma	19 (19)	13 (14)
Immobilization	15 (15)	9 (9)
Delivery	4 (4)	3 (3)
Oral contraceptives	2 (2)	4 (4)
Weight 100 kg or more	6 (6)	7 (7)
\geq 2 of these	12 (12)	10 (10)

Table 3 Recurrences of thromboembolism during the study

	LMWH group (n=98)	OA group (n=95)
	no. of patients (time)	
Secondary prophylaxis (3 months)		
Total events	2	7
Recurrence of DVT	2 (weeks 7,12)	3 (weeks 8, 8, 9)
Pulmonary embolism		4* (weeks 2, 3, 6, 8)
Surveillance period (9 months)		
Total events	5	2
Recurrence of DVT	3 (months 5, 7, 8)	1 (month 12)
Pulmonary embolism	2 (months 5, 8)	1 (month 8)
Total (12 months)	7	9

* One fatal pulmonary embolus.

Table 4 Bleeding complications during the study

	LMWH group (n=98)	OA group (n=95)
	no. of patients (time)	
Secondary prophylaxis (3 months)		
Major bleeding		
Gastrointestinal	1 (week 5)	1 (week 8)
Gross hematuria		
Minor bleeding		
Hematuria	2* (weeks 2, 12)	4 (weeks 2, 2, 3, 8)
Gingival		2 (weeks 5, 9)
Epistaxis	1 (week 6)	
Surveillance period (9 months)		
Major bleeding		
Gastrointestinal	1** (month 6)	
Total (12 months)	5	7

* Carcinoma of bladder in 1 patient.

** The patient had metastatic cancer.

mild and transient decrease in the platelet count (to $90 \times 10^9/l$) during initial treatment. A mild and transient thrombocytopenia (with a platelet count of $79-90 \times 10^9/l$) was also observed in 2 patients during secondary prophylaxis, in 1 receiving LMWH between day 11 and 17 and in 1 on acenocoumarol between day 11 and 13.

Deaths

Five patients in the LMWH group and 6 in the OA group died during the one year follow-up. The causes of death included metastatic cancer, pulmonary embolus and heart failure (Table 5).

Table 5 Causes of death in the treatment groups

	LMWH group n (week)	OA group n (week)
Metastatic cancer	4 (6, 8, 17, 37)	3 (3, 24, 25)
Pulmonary embolus		1 (8)
Heart failure	1 (17)	2 (25, 28)

Discussion

It has been shown in a randomized trial that UFH administered s.c. for 3 months in a dose adjusted to prolong the mid-interval activated partial thromboplastin time (APTT) to 1.5 times the control values provides an effective alternative to warfarin and is associated with a lower risk of bleeding (1). However, in clinical practice adjusted-dose unfractionated heparin has not replaced oral anticoagulants for secondary prophylaxis of DVT, probably because it requires monitoring during the first days of treatment and twice-daily dosing. Physicians also may be reluctant to use UFH for longer period of time fearing osteoporosis.

The long-term use of LMWHs has been evaluated in three recent studies. Monreal et al. (17) compared UFH (10,000 IU twice daily s.c.) to LMWH (dalteparin, 5000 anti-Xa IU twice daily s.c.). Both drugs were administered for a period of 3-6 months to prevent venous thromboembolism in patients with DVT and contraindications to oral anticoagulants, such as age over 80, a history of recent bleeding, recent neurosurgery or chronic alcoholism. No recurrent symptomatic DVT was observed during the first three months of treatment but two patients in the unfractionated heparin group developed pulmonary embolism. No major bleeding was reported in either group. Seven patients developed osteoporotic spinal fractures, 6 of the 40 patients on unfractionated heparin and 1 of the 40 on LMWH. Two groups of investigators (24, 25) compared LMWH to warfarin for secondary prophylaxis of DVT after a 10-day initial therapy with UFH. In a clinical trial conducted by Pini et al. (24), LMWH (enoxaparin) was used in a fixed dose of 40 mg (4000 anti-Xa IU) once daily s.c. Das et al. (25) used LMWH (dalteparin) in a fixed dose of 5000 anti-Xa IU once daily s.c. In both studies there was a small (non-significant) trend to a higher incidence of recurrent venous thromboembolism and a more convincing evidence of fewer bleeding complications in the LMWH group. As suggested by the authors, a higher dose of LMWH for the secondary prophylaxis could lead to improved efficacy and still maintain safety.

In the present study, LMWH (nadroparin) was administered for both the initial therapy and the secondary prevention of recurrent thromboembolism in a dose adjusted to body weight. The 10-day initial treatment with subcutaneous nadroparin given twice daily and administered jointly with acenocoumarol for 4 days has been evaluated in our previous trial and has been shown to be effective and safe anticoagulation in patients with acute DVT (9). The optimal duration of the initial heparin therapy in patients with venous thromboembolism has not been completely resolved. Short courses of heparin (4 to 7 days) with oral anticoagulation commenced on the first or second day are currently used in many hospitals because of economic factors. However, this approach may not be appropriate for patients with massive iliofemoral vein thrombosis or pulmonary embolism (26). On the other hand, treatment with LMWH for a period longer than 10 days was recommended in one study on the basis of phlebographic findings (27).

In the vast majority of our patients the LMWH dose for secondary prophylaxis was larger than the fixed dose administered by Pini et al. (24). There was a lower incidence of recurrent thromboembolism during the 3-month period of secondary prophylaxis in patients on LMWH compared to those on acenocoumarol, but the difference between the

two groups is not significant. This trend, however, was not observed during the 9-month surveillance period, most likely because the two groups were not balanced with respect to the prolonged administration of an anticoagulant drug. Of the 5 new episodes of venous thromboembolism observed in the LMWH group during the surveillance period, 4 occurred in patients with idiopathic DVT after nadroparin withdrawal. During the combined secondary prophylaxis and surveillance period, 7.1% of patients in the LMWH group had recurrences, as compared with 9.5% in the OA group; this difference is not significant.

The incidence of major bleedings during the 3-month period of secondary prophylaxis was low in both groups, 1 in the LMWH group and 1 in the OA group. As in the two previously published trials (24, 25) minor bleedings were fewer in patients receiving LMWH than in patients on acenocoumarol (3.1% versus 6.3%), and this was a non-significant difference. These results indicate the LMWH is a safe antithrombotic drug.

The number of deaths was similar in the two treatment groups. Seven patients died of metastatic cancer, 4 in the LMWH group and 3 in the OA group. Thus, our data are consistent with those of Pini et al. (18) and do not support the opinion that the treatment with LMWH could exert a favourable effect on cancer progression (28). However, the number of cancer patients included in this study was relatively small.

We did not perform a cost analysis comparing LMWH and acenocoumarol for the 3-month secondary prophylaxis of DVT. LMWHs are more expensive than acenocoumarol or warfarin. However, as estimated by Das et al. (25), the total cost may be lower for patients treated with LMWH than for those receiving OA, mainly due to a difference in inpatient days. In the trial conducted by these authors, the period of hospitalization was reduced by an average of 3 days for patients allocated to receive LMWH.

Our study has two limitations: 1) The treatment groups were not balanced with respect to the continuation of secondary prophylaxis beyond the planned 3-month period. Following the directions of treating physicians, 43% of acenocoumarol treated patients continued oral anticoagulant therapy for a period longer than 3 months, whereas the treatment with nadroparin was prolonged only in 8% of patients in the LMWH group. Similar imbalance appeared in the study of Pini et al. (24). The 3-month secondary prophylaxis is currently considered too short for patients with idiopathic DVT or continuing risk factor (19, 29-31). This view is supported by the study of Prandoni et al. (32) who reported a recurrence rate of 24% in patients with idiopathic DVT as compared with 4.8% in patients with secondary thrombosis, during a mean follow-up of 80 weeks. 2) The sample size was relatively small. Therefore a minor difference between the treatment groups in the incidence of major bleeding events may have remained undetected.

Bearing these limitations in mind, we may conclude that subcutaneous injections of nadroparin in a dose of 85 anti-Xa IU/kg bw. (225 anti-Xa ICU/kg) once a day, i.e. half of a daily dose administered during the initial treatment, are safe and at least as effective as treatment with acenocoumarol in the secondary prophylaxis of DVT. It seems most unlikely that LMWHs shall replace warfarin or acenocoumarol in most patients with DVT due to the greater convenience of oral therapy. However, subcutaneous weight-adjusted dose LMWH may be an useful alternative to oral anticoagulants in selected groups of patients. Since the LMWH administration does not require laboratory control, it could be a treatment of choice in patients from geographically remote areas in whom monitoring of oral anticoagulant treatment is unavailable or unpractical. The best candidates for secondary prophylaxis with LMWH are patients with transient risk factors for DVT for whom an anticoagulation for a period not longer than 3 months could be adequate

and a regular laboratory monitoring is a hardship. Long-term treatment with LMWH can also be recommended for patients with a relative contraindication to oral anticoagulants, such as chronic alcoholism or pregnancy. The dose of LMWH in pregnant women should probably be higher than that used in our study. This remains to be estimated in a future clinical trial.

Acknowledgement

The authors would like to thank Dr. H. G. Vanhaeren (Sanofi Winthrop, Paris) and Mrs B. Roszkowska (Sanofi Biocom, Warsaw) for their help in the organization of the trial.

Appendix

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References

- Hull R, Delmore T, Carter C, Hirsh J, Genton E, Gent M, Turpie G. Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. *N Engl J Med* 1982; 306: 189-94.
- Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; 68: 122-40.
- Leizorowicz A, Haugh MC, Chapuis F-R, Samama MM, Boissel J-P. Low molecular weight heparin in prevention of perioperative thrombosis. *Brit Med J* 1992; 305: 913-20.
- Green D, Hirsh J, Heit J, Prins M, Davidson B, Lensing AWA. Low molecular weight heparin: a critical analysis of clinical trials. *Pharmacol Rev* 1994; 46: 89-109.
- Bratt G, Aberg W, Johansson M, Törnebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). *Thromb Haemost* 1990; 64: 506-10.
- Duroux P, Beclere A. A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost* 1991; 65: 251-6.
- Hull RD, Raskob GE, Pineo GE, Green D, Trowbridge AA, Elliott CG, Lerner RG, Hall J, Sparling T, Brettell HR, Norton J, Carter CJ, George R, Merli G, Ward J, Mayo W, Rosenbloom D, Brant R. Subcutaneous low-molecular weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992; 326: 975-82.
- Prandoni P, Lensing AWA, Büller HR, Carta M, Cogo A, Vigo M, Casara D, Ruol A, ten Cate JW. Comparison of subcutaneous low-molecular weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet* 1992; 339: 441-5.
- Lopaciuk S, Meissner AJ, Filipiecki S, Zawilska K, Sowier J, Ciesielski L, Bielawiec M, Glowinski S, Czestochowska E. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. *Thromb Haemost* 1992; 68: 14-8.
- Lindmarker P, Holmström M, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost* 1994; 72: 186-90.
- Koopman MMW, Prandoni P, Piovella F, Ockelford PA, Brandjes DPM, van der Meer J, Gallus AS, Simonneau G, Chesterman CH, Prins MH, Bossuyt PMM, de Haes H, van den Belt AGM, Sagnard L, d'Azemar P, Büller HR, for the TASSMAN Study Group. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996; 334: 682-7.
- Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, Turpie AG, Demers C, Kovacs M, Geerts W, Kassis J, Desjardins L, Cusson J, Cruickshank M, Powers P, Brien W, Haley S, Willian A. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996; 334: 677-81.
- Simonneau G, Sors H, Charbonnier B, Page Y, Laaban J-P, Azarian R, Laurent M, Hirsch J-L, Ferrari E, Bosson J-L, Mottier D, Beau B. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997; 337: 663-9.
- The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997; 337: 657-62.
- Hirsh J, Levine MN. Low molecular weight heparin. *Blood* 1992; 79: 1-17.
- Melissari E, Muray WJG, Das S, Wilson NV, Philip M, Kakkar VV. Does low molecular weight heparin have a role in the development of osteoporosis? *Thromb Haemost* 1993; 69: 646.
- Monreal M, Lafoz E, Olive A del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. *Thromb Haemost* 1994; 71: 7-11.
- Lensing AW, Hirsh J, Büller HR. Diagnosis of Venous Thrombosis. In: Hemostasis and Thrombosis. Basic Principles and Clinical Practice. Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. Philadelphia: J. B. Lippincott 1993; 1297-321.
- Hirsh J, Hoak J. Management of deep vein thrombosis and pulmonary embolism. *Circulation* 1996; 93: 2212-45.
- Hirsh J, Bettman M, Coates G, Hull RD. Diagnosis of Pulmonary Embolism. In: Hemostasis and Thrombosis. Basic Principles and Clinical Practice. Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. Philadelphia: J. B. Lippincott 1993; 1322-30.
- Griffiths E, Dzik WH. Assays for heparin-induced thrombocytopenia. *Transfusion Med* 1997; 7: 1-11.
- Hull R, Hirsh J, Carter C, England C, Gent M, Turpie AGG, McLoughlin D, Dodd P, Thomas M, Raskob G, Ockelford P. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med* 1982; 307: 1676-81.
- Holmgren K, Andersson G, Fagrell B, Johnsson H, Ljungberg B, Nilsson E, Wilhelmsson S, Zetterquist S. One-month versus six-month therapy with oral anticoagulants after symptomatic deep vein thrombosis. *Acta Med Scand* 1985; 218: 279-84.
- Pini M, Alello S, Manotti C, Pattacini C, Quintavalla R, Poli T, Tagliaferri A, Dettori AG. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. *Thromb Haemost* 1994; 72: 191-7.
- Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. *Word J Surg* 1996; 20: 521-7.
- Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 1: Heparin. *Circulation* 1994; 89: 1449-68.
- Kirchmaier CM, Lindhoff-Last E, Rübesam D, Scharrer I, Vigh Zs, Mosch G, Wolf H, Breddin HK. Regression of deep vein thrombosis by i.v.-administration of a low molecular weight heparin – results of a pilot study. *Thromb Res* 1994; 73: 337-48.
- Green D, Hull RD, Brant R, Pineo GF. Lower mortality in cancer patients treated with low-molecular-weight heparin versus standard heparin. *Lancet* 1992; 339: 1476.

29. Schulman S, Rhedin A-S, Lindmarker P, Carlsson A, Lärfars G, Nicol P, Loogna E, Svensson E, Ljungberg B, Walter H, Viering S, Nordlander S, Leijd B, Jonsson K-A, Hjorth M, Linder O, Boberg J. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995; 332: 1661-5.
30. Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, Geerts W, LeClerc J, Neemeh J, Powers P. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemost* 1995; 74: 606-11.
31. Prandoni P, Lensing AWA, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins M.H. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; 125: 1-7.
32. Prandoni P, Lensing AW, Büller HR, Cogo A, Prins MH, Cattelan AM, Cuppini S, Noventa F, ten Cate JW. Deep-vein thrombosis and the incidence of subsequent cancer. *N Engl J Med* 1992; 327: 1128-33.

Received June 11, 1998 Accepted after resubmission September 22, 1998