

Home Treatment of Deep Venous Thrombosis With Low Molecular Weight Heparin: Long-Term Incidence of Recurrent Venous Thromboembolism

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Outpatient treatment of deep venous thrombosis (DVT) with low molecular weight heparin (LMWH) seems as safe and effective as inpatient treatment with unfractionated heparin (UFH). However, most of the randomized trials comparing a LMWH with UFH described clinical outcomes within 3–6 months. The long-term incidence of recurrent VTE after treatment of DVT with LMWH remains to be established. The primary objective of this retrospective study was to document the long-term incidence of recurrent venous thromboembolism (VTE) in patients with DVT treated with a LMWH, nadroparin in an outpatient basis. The patients were evaluated 46 months after inclusion in two cohorts comparing home treatment with nadroparin ($n = 130$) with in-hospital treatment with intravenous UFH ($n = 149$). More than 60% of the patients in the nadroparin group could be treated at home, either entirely or after a short stay in hospital. The age-adjusted thrombosis-free survival was not statistically significant between nadroparin and UFH-treated patients ($P = 0.084$). There was a nonsignificant trend favoring nadroparin as compared with UFH. The hazard ratio (HR) for recurrent VTE in the nadroparin group with respect to the UFH group was 0.44 (95% confidence interval, 0.17–1.12). No significant differences were observed in overall mortality or major hemorrhage between the two treatment groups. Our study suggests that home treatment of DVT with LMWH is at least as effective and safe as in-hospital UFH after a long-term follow-up period. *Am. J. Hematol.* 67:10–14, 2001. © 2001 Wiley-Liss, Inc.

Key words: deep venous thrombosis; home treatment; low molecular weight heparin; recurrent venous thromboembolism; long-term follow-up

INTRODUCTION

The major concern in the management of deep venous thrombosis (DVT) is recurrent venous thromboembolism (VTE) and post-thrombotic syndrome. Anticoagulant therapy is the treatment of choice for most patients with DVT. Acute DVT is usually treated with a five-to-seven day course of intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH), followed by at least three months of oral anticoagulant therapy [1–3]. LMWH have the potential advantage of allowing patients with uncomplicated DVT to be treated at home rather than in the hospital. Indeed, outpatient treatment with LMWH seems as safe and effective as inpatient treatment with UFH [4,5]. However, most of

the randomized trials comparing a LMWH with UFH described clinical outcomes within 3–6 months [6,7]. Although the highest rates of recurrent VTE are observed within the first 6 months after the initial episode, some patients have persistent risk factors that precipitate recurrences when oral anticoagulant therapy is stopped [8,9]. The long-term incidence of recurrent VTE after treatment of DVT with LMWH remains to be estab-

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lished. The purpose of this study was to determine the incidence of recurrent VTE after an initial episode of DVT, comparing initial treatment with in-hospital UFH with treatment LMWH in an outpatient basis, after a long-term follow-up period.

PATIENTS AND METHODS

Patients

This was a retrospective analysis of two cohorts of patients with acute, symptomatic DVT referred to the emergency department of the Hospital Lluís Alcanyis. The first cohort started in July 1995, and the last patient was included in July 1999. Most of the patients were recruited from a previously reported prospective clinical trial using subcutaneous Nadroparin-Ca (Laboratoires Choay, Paris, France) in the initial treatment of DVT in an outpatient basis [10]. The second cohort started in January 1986, and the last patient was included in December 1996. All patients included in this second cohort were recruited from a previous retrospective study using in-hospital intravenous UFH in the initial treatment of DVT [11].

Patients were eligible for the study if DVT was confirmed by duplex ultrasonography or venography. Patients were excluded from the study if they had concurrent symptomatic pulmonary embolism (PE) or if they received inadequate anticoagulant treatment. Dose adjustments were made according to the activated partial thromboplastin time (APTT) for patients treated with UFH. Patients treated with nadroparin received twice-daily injections, in doses adjusted for the patient's weight. Patients weighing less than 50 kg received a total daily dose of 8,200 International Factor Xa Inhibitory Units per liter; those weighing between 50 and 60 kg, 10,000 IU; those weighing between 60 and 70 kg, 12,300 IU; those weighing between 70 and 80 kg, 14,500 IU; and those weighing over 80 kg, 16,400 IU. There was no laboratory monitoring. Patients treated with nadroparin were allowed to go home immediately after diagnosis or to be discharged after a short hospital stay [10]. At least 5 days of treatment with UFH or nadroparin was required. Treatment with acenocoumarol was begun 2 days before discontinuing UFH or nadroparin and continued for a total of 6 months, unless the persistence of risk factors required its continuation beyond that period.

All patients with recurrent VTE were reassessed in our clinical center on an outpatient basis. Each visit included history taking and physical examination. Information was obtained on possible risk factors for VTE. These included previous DVT/PE, immobilization, surgery, trauma, concurrent medical conditions such as pregnancy or infection, and malignancy. Idiopathic VTE was considered when DVT and/or PE occurred without any of these risk factors within preceding 6 months. Secondary

VTE was considered when thromboembolism occurred within 6 months of at least one of these risk factors.

Definition of recurrent VTE included three distinct entities: (1) the development of new thrombi in initially involved limbs, (2) the development of a contralateral DVT, and (3) PE suspected in a patient on the basis of clinical symptoms or signs and confirmed by lung scanning.

Patients records and data from the Hospital Discharge Registry as well as outpatient data were used for documenting recurrent VTE and deaths.

Coagulation Tests

At the end of anticoagulant treatment (at least 15 days after its completion) natural and acquired inhibitors of hemostasis were studied in most of the patients under age 50. Blood samples were subject to a thrombophilia screen which included prothrombin time, APTT, thrombin time, antithrombin III and protein C activity, free and total protein S, lupus anticoagulant screen, plasminogen activity, and IgG and IgM anticardiolipin antibody assays. Testing for APC resistance was not performed in our laboratory until 1995. Most of the patients diagnosed of recurrent VTE, even those with the first thrombotic episode before 1995, have been subsequently invited to attend for a new blood sampling and have been screened for APC resistance.

Statistical Analysis

Chi-square analysis and Student's *t*-test were used for comparison of category of variables and groups. $P < 0.05$ was considered statistically significant. Recurrent VTE was calculated as cumulative incidence (percentage of events). Because patients from the two cohort groups were followed for different times, we used a survival analysis with right-censored data. Kaplan-Meier analysis and the log-rank test for comparison were used for time-to-event analysis for recurrent VTE. Cox's proportional-hazards regression model was used to assess the effect of different variables on time to recurrent VTE. All statistical analyses were performed by means of SPSS 7.5 for Windows95.

RESULTS

The recruitment of patients in the nadroparin cohort group began in July 1995 and was completed in July 1999. During this period, we screened 213 patients with acute DVT. Of these, 83 were excluded for the following reasons: 65 patients with concurrent PE, 13 treated with UFH, and 5 treated with other LMWH. The remaining 130 patients were included in the study. Ambulatory treatment was feasible in 82 patients (64%). Among those who were treated at home, 58 patients (45%) were not hospitalized at all and another 24 patients (19%) were

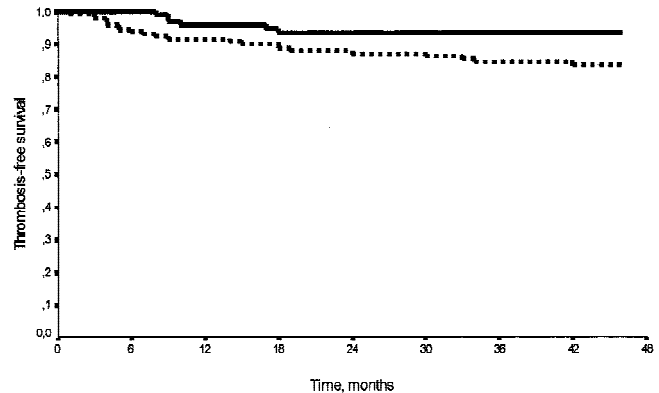
TABLE I. Demographic and Clinical Characteristics of the Study Population (n = 279)

	UFH (n = 149)	Nadroparin (n = 130)
Age (yrs) (median ± SD)	59.4 ± 16.2	67.5 ± 12.9
Sex (M/F)	86/63	76/54
	no. (%)	no. (%)
Localization		
Calf only	32 (21.5)	25 (19.2)
Proximal ± calf	117 (78.5)	105 (80.8)
Known risk factors		
Idiopathic	69 (46.3)	63 (48.5)
Secondary	80 (53.7)	67 (51.5)
Immobilization	11 (7.4)	8 (6.2)
Surgery	31 (20.8)	21 (16.1)
Trauma	13 (8.7)	10 (7.7)
Concurrent medical process	14 (9.4)	9 (6.9)
Previous VTE	5 (3.4)	3 (2.3)
Malignancy	6 (4.0)	16 (12.3)

discharged during the first two days of treatment. The remaining 46 patients (36%) received treatment with nadroparin in hospital.

In the UFH cohort group, a total of 290 patients had an episode of VTE between January 1986 and December 1996. Of these, 141 patients were excluded for the analysis because they had a suspected PE. The remaining 149 patients with acute DVT were examined.

Baseline characteristics of the treatment groups are shown in Table I. The treatment groups were similar at entry, except that patients treated with nadroparin were significantly older than patients treated with UFH ($P < 0.0001$). Because this difference could influence thrombosis-free survival, the effect of age was controlled using Cox's proportional-hazards regression model. The starting point was considered as the time of diagnosis of DVT. As the maximum duration of follow-up in the group of nadroparin was 46 months, this period was considered as the maximum censored survival time. Therefore, all recurrent episodes occurred after 46 months of follow-up in the group of patients treated with UFH were right-censored and not computed for the analysis. The mean duration of follow-up was 21.6 months for the group of patients treated with nadroparin and 35.0 months for those treated with UFH. During the observation period, 28 (10%) episodes of recurrent VTE were diagnosed in both groups, of these 16 (5.7%) occurred within 1 year after the initial treatment. A recurrent VTE was observed in 6 patients treated with nadroparin (4.7%) and 22 patients treated with UFH (14.7%) ($P = 0.15$). Although there were differences in favor of LMWH, thrombosis-free survival was not statistically different between both treatment groups ($P = 0.084$) (Fig. 1). In a proportional hazard model the hazard ratio (HR) for recurrent VTE in the nadroparin group with respect to the UFH group was 0.44 (95% CI 0.17–1.12). On the other hand, during the first 6 months of follow-up,

**Fig. 1. Thrombosis-free survival comparing nadroparin (—) and UFH (···).**

there was a significant reduction in the risk of recurrent VTE in patients treated with nadroparin compared to those treated with UFH ($P = 0.006$) (Fig. 1). Finally, the risk for recurrent VTE was not affected by other variables such as age at inclusion, gender, or known malignant disease at inclusion.

Of the 6 thrombotic recurrences in the nadroparin group, 5 involved ipsilateral DVT and 1 involved PE. Of the 22 events in the UFH group, 10 involved ipsilateral DVT, 3 involved contralateral DVT, and 9 involved PE. None of these patients died due to the recurrent VTE. Three patients with recurrent VTE were diagnosed with malignancy at inclusion (two patients in the nadroparin group and one patient in the UFH group). These three patients died after the second thrombotic event. During follow-up one patient from the UFH group with recurrent VTE developed lung cancer.

The thrombophilia screen could be performed in 12 of the 15 patients younger than 50 years at inclusion (11.5%) in the nadroparin group. Four hemostasis abnormalities were found (30%): APC resistance (two) and protein C deficiency (two). Of these, only the two patients with protein C deficiency received permanent oral anticoagulant treatment. None of these patients with inherited thrombophilia have suffered recurrent VTE during the observation period. On the other hand, none of the six patients with recurrent VTE in the nadroparin group showed hemostasis abnormalities. In the UFH group, the thrombophilia screen was performed, at least partially, in all 37 patients aged under 50 years at inclusion (25%). Six hemostasis abnormalities were found (16.2%): APC resistance (three), deficiency of protein C (one), deficiency of protein S (one), and lupus anticoagulant (one). All these patients have suffered a recurrent event and received long-term anticoagulant therapy.

There was no significant difference in the incidence of major hemorrhage between the two treatment groups during the initial treatment with nadroparin or UFH. The major hemorrhages consisted of one episode of gastro-

intestinal hemorrhage in a patient also receiving nonsteroidal drugs, an episode of hemoptysis requiring hospitalization probably related to pulmonary hypertension in the group of patients treated with nadroparin (1.5%), and an episode of retroperitoneal hematoma in the group of patients treated with UFH (0.7%) ($P = 0.9$). During oral anticoagulant therapy, there were two episodes of hemorrhage (an episode of gastrointestinal bleeding and an episode of hematuria) in the nadroparin group (1.5%) and four episodes in the UFH group (three episodes of hematuria, and an episode of skin hematomas) (2.7%) ($P = 0.8$). None of the hemorrhages were fatal.

During the follow-up period, 17 patients receiving UFH died, as compared with 11 patients receiving nadroparin ($P = 0.7$).

DISCUSSION

Recent randomized trials have shown that home treatment with LMWH in patients with DVT is as safe and effective as in-hospital treatment with UFH [4,5]. Moreover, this therapeutic alternative is feasible in most of the patients presenting to hospitals with DVT [10,12]. Although home treatment with LMWH seems to be as effective as in-hospital UFH in reducing the risk for recurrent VTE within 6 months after inclusion, the long-term efficacy remains to be established. Our study was designed to evaluate if home treatment of DVT with LMWH was at least as effective as in-hospital UFH in decreasing the incidence of recurrent VTE, after a longer follow-up period. Our study assessed the hospital incidence of recurrent VTE in two large treatment groups: a cohort of patients treated in-hospital with UFH and a cohort of patients treated with nadroparin primarily at home. In our series, more than 60% of patients could be treated at home with nadroparin, either entirely or after a short stay in hospital. This proportion of patients eligible for the outpatient treatment of DVT is in accordance with other series from Western countries [12,13].

Because it was a retrospective study, with two cohorts with different observation periods, care was taken to minimize the potential for bias. For this study our patients were consecutive from a well-defined geographic population and we used predetermined methods for outcomes. Demographic and clinical characteristics were comparable between groups except for age. The effect of age was controlled using Cox's proportional-hazards regression model. This should ensure that our data are valid; however, randomized clinical trials to prove the long-term efficacy and safety of home treatment of DVT with LMWH should be performed.

The mean age of the patients treated with nadroparin group was significantly higher than the mean age of the patients treated with UFH. This was probably due to the

fact that the Spanish population ages and the mean age of our geographic population were higher in the more recent nadroparin patient cohort than in the UFH patient cohort. The age-adjusted incidence of recurrent VTE during almost 4 years after inclusion was not statistically significant between nadroparin and UFH-treated patients. In our study, there was a nonsignificant trend favoring nadroparin as compared with UFH. In addition, during the first 6 months of follow-up, there was a significant reduction in the risk of recurrent VTE in patients treated with nadroparin compared to those treated with UFH. Other studies have also reported that treatment with LMWH decreases the risk for recurrent VTE within 3 months after inclusion [14]. It is generally accepted that subtherapeutic aPTT during UFH therapy is associated with a higher risk of recurrent VTE [3]. On the other hand, it seems logical that LMWH might reduce early recurrences due its longer half-life and a more predictable anticoagulant response to a fixed dose than does UFH [15].

The rates of recurrent VTE were low and similar in the two treatment groups. This low incidence of recurrence is in accordance with previous studies [11,16,17]. In our study, the cumulative incidences of recurrent VTE after 12 and 46 months were 5.7% and 10%, respectively. These findings are consistent with those of recent studies reporting the highest risk of recurrence during the following 2 years after cessation of anticoagulant therapy [18]. Thus, our data do not provide evidence that the risk for recurrent VTE remains high for many years as had been reported by other investigators [19].

We performed the thrombophilia screen in a minority of patients due to the advanced age of our study population. Despite this fact, we found hemostasis abnormalities in about 20% of patients younger than 50 years. In addition, this percentage increased up to 55% for patients younger than 50 years with recurrent VTE. Therefore, thrombophilia screen seems highly recommended in patients younger than 50 years, especially in those with recurrent VTE.

Other studies have reported a lower total mortality with LMWH compared with UFH during a period of 3–6 months [7]. In our study there was not difference between nadroparin and UFH regarding overall mortality during the observation period.

In conclusion, our study suggests that home treatment of DVT with LMWH is at least as effective and safe as in-hospital UFH after a long-term follow-up period. On the basis of its efficacy and safety, convenience for the patients, and substantial reduction in the cost to the health care system, home treatment with LMWH seems to be the preferred therapy for most of the patients with DVT.

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