Out of hospital treatment with subcutaneous low molecular weight heparin in patients with acute deep-vein thrombosis: a prospective study in daily practice

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Background and Objectives. Clinical trials have demonstrated that initial outpatient treatment is safe and effective in patients with deep vein thrombosis (DVT). Considering the relative lack of literature-based evidence on outpatient low molecular weight heparin (LMWH) treatment in daily practice this study prospectively evaluated the implementation of a protocol for full outpatient treatment of DVT in a non-teaching hospital.

Design and Methods. Consecutive patients with objectively demonstrated DVT were treated on an outpatient basis with subcutaneous nadroparin injections for at least 5 days and oral anticoagulant treatment for at least 3 months.

Results. In 294 of 309 (95%) consecutive patients with proven DVT, nadroparin could be started on a fully outpatient basis. During initial LMWH treatment one patient had to be hospitalized because of objectively proven pulmonary embolism (PE), and one patient developed a major bleeding complication. Overall, during 3 months follow-up recurrent venous thromboembolism (VTE) occurred in nine patients (3.1%; 95 CI 1.1 to 5.1), four patients experienced a major non-fatal hemorrhage (1.4%; 95 CI 0.04 to 2.7) and ten patients died (3.4%; 95% CI 1.3 to 5.5) of whom seven with disseminated malignancy, but none of fatal PE.

Interpretation and Conclusions. Out of hospital initiation of anticoagulant treatment with LMWH is safe and effective in the overall majority of patients (95%) with objectively proven DVT. We believe that these results are relevant to both clinicians and health care providers in view of the feasibility of home treatment in nearly all patients.

Key words: deep vein thrombosis, outpatient treatment, low molecular weight heparin, implementation

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Administration of heparin has been shown to be essential in the initial treatment of deep venous thrombosis (DVT).[1] Major hemorrhage is the most important side effect of heparin treatment and has been reported in up to 4-5% of cases in routine clinical practice.[2,3] Importantly, proper use of intravenous heparin in daily practice is challenged by the need for frequent monitoring of the activated partial thromboplastin time (aPTT) and interruption of heparin infusion.[2] Treatment of DVT with subcutaneous low molecular weight heparin (LMWH) once or twice daily has been shown to be at least as safe and effective as treatment with intravenous unfractionated heparin.[4,5] The properties of LMWH, which include excellent bioavailability, long half-life and predictable anticoagulant response, preclude the need for intensive laboratory controls[6,7] which has led to the opportunity of starting anticoagulant treatment on an outpatient basis. Furthermore, home treatment has been shown to be cost-effective and to lead to a high level of patient satisfaction and to a better quality of life than that associated with starting treatment in hospital.[8,9] Two large clinical trials, performed in tertiary referral centers, demonstrated that initial outpatient treatment with LMWH is safe and effective.[8,10] However, both studies were carried out in selected populations of patients and their results might therefore be less applicable in daily clinical practice. In the first study[8] 1491 of 2230 potentially eligible patients with proximal DVT (67%) were excluded for various reasons. Furthermore, in this study only 120 of 247 patients (49%) randomized to receive LMWH were treated on a complete outpatient basis. In the other study[10] a minority of 72 of 202 patients (36%) receiving LMWH were completely treated at home, while almost half of the

included patients had to be hospitalized for at least 2 days. Recently, several prospective cohort studies have evaluated eligibility for home treatment in routine clinical practice.[9,11–16] In most of these studies a relatively small number of patients were included (range 71 to 130 patients).[9,11,13,15,16] Moreover, 20% to 70% of patients were not treated on a full outpatient basis for various reasons e.g. medical reasons, logistics and home care situation.[9,12–16]

The purpose of the present study was to evaluate a daily practice-based protocol for full outpatient treatment of DVT in consecutive patients with objectively demonstrated DVT referred to a non-teaching hospital.

Design and Methods

Between March 1997 and March 2002 consecutive patients presenting with suspected DVT in the Veghel region were sent to the Emergency Department of Bernhoven Hospital, Veghel, The Netherlands, a hospital with 290 beds and a catchment population of 120,000 inhabitants. Compression ultrasonography (CUS) was used to confirm or exclude the diagnosis of DVT.[17] If DVT could not be confirmed by CUS on day 1, the CUS was repeated on day 7. All patients with objectively confirmed DVT were considered eligible for outpatient treatment with a LMWH according to a standardized protocol shown in the flow chart (Figure 1). D-dimer analysis was not used in the diagnostic work-up of our patients. Hospital admission was indicated if there was a clinical suspicion of pulmonary embolism (PE), if patients suffered from severe co-morbidity requiring in-hospital medical supervision, or if they were pregnant. Informed consent was obtained from all patients. The study was approved by the Institutional Review Board of Bernhoven Hospital, Veghel, The Netherlands.

Treatment regimen

Initial treatment with LMWH was started in the Emergency Department and consisted of twice daily subcutaneous nadroparin (Fraxiparine® 9,500 IU anti Xa/mL) injections of 0.4 mL (bodyweight <50 kg), 0.6 mL (bodyweight 50 to 70 kg), or 0.8 mL (bodyweight >70 kg)for at least 5 days. The decision to change from twice daily to once daily administration of LMWH was made by local hospital consensus. This decision was based on the results of Charbonnier's study[5] and after its introduction in The Netherlands (1st of January, 2000), the treatment regimen was changed to Fraxodi® (19,000 IU anti-Xa/ mL), 0.6 mL (bodyweight <70 kg), or 0.8 mL (bodyweight > 70 kg), once daily[5] for at least five days. All patients were treated with coumarin drugs according to the consensus of the Dutch Thrombosis Services, i.e. patients with proven DVT received subcutaneous injections with therapeutic nadroparin until the International normalized Ratio (INR) was maintained within the target therapeutic range (INR 2.0 to 3.0) for at least two consecutive days. On the same day as the first dose of LMWH acenocoumarol was started according to a standardized loading scheme (i.e. 8 mg on the first day, and 4 mg on the second day) and the INR was checked on the third day. Treatment with acenocoumarol was continued for at least 3 months. The treatment duration was adjusted in patients with a medical history of venous thromboembolism and in those who suffered from complications during their treatment period.

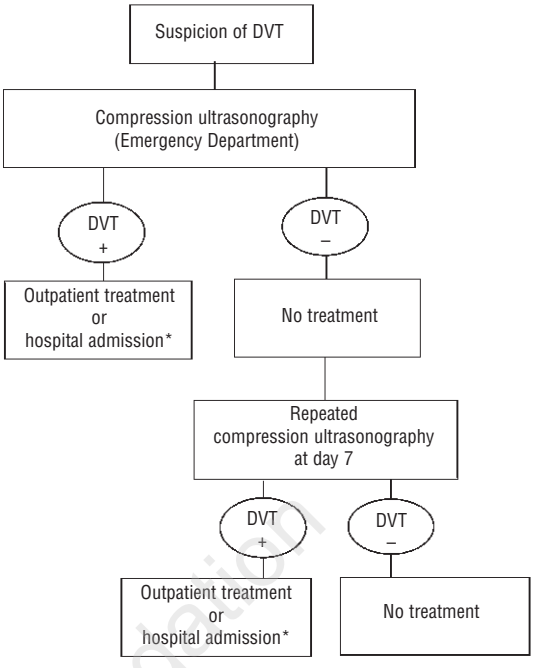

Figure 1. **Flow chart for the management of a patient presenting at the Emergency Department with suspected DVT.** ***In case of suspected pulmonary embolism, severe comorbidity or pregnancy. DVT: deep vein thrombosis.***

Before hospital discharge the following appointments were arranged for all patients (Figure 2): (i) on the day of presentation, the patient received a prescription for compression stockings; (ii) in the case of severe edema an appointment for compression therapy was made at the Dermatology outpatient clinic within 3 days; (iii) the INR was checked by the Thrombosis Service, Veghel on day 3 and the dose of acenocoumarol on subsequent days was determined; (iv) a routine 3-month follow up visit at the outpatient clinic was scheduled. All patients received a brochure with information on outpatient treatment with LMWH. During home treatment the general practitioner took care of the patient. Daily subcutaneous LMWH injections were administered at the general practitioner's office. Patients were instructed to contact their general practitioner or internist immediately if they developed clinical signs of recurrent DVT or PE or if a bleeding complication occurred.

Checklist for patients with a clinical suspicion of DVT presenting at the Emergency Department

1. Confirm DVT by compression ultrasonography by a radiologist

After confirmation:

2. Start initial treatment with nadroparin;

3. Plan compression therapy by a dermatologist within 3 days;

4. Check the INR on the third day;

5. Plan routine follow up in the Outpatient Department after 3 months;

6. Provide the patient with an information brochure;

7. Inform the general practitioner by telephone or fax

Figure 2. Checklist for patients with a clinical suspicion of DVT presenting at the Emergency Department.

Table 1. Patients' characteristics (n=294) at presentation to the Emergency Department.

Characteristics	*All included patients n=294*	Patients receiving *once daily LMWH n=149*	Patients receiving *twice daily LMWH n=145*
Sex (Male/Female)	135 (46%)/ 159 (54%)	67(45%)/ 82(55%)	68 (45%)/ 77(53%)
Age (SD)	56.6 (SD 18)	56.6 (SD 18)	56.1 (SD 19)
Localization			
Proximal DVT	238 (81%)	105 (70%)	133 (92%)
Isolated calf vein thrombosis	51 (17%)	39 (26%)	12 (8%)
Thrombosis of upper extremity	5 (2%)	5 (4%)	0 (0%)
History of DVT	57 (19%)	21 (14%)	36 (25%)
Positive family history	68(23%)	31 (21 %)	37 (26%)
Malignancy	37 (13%)	15 (10%)	22 (15%)

Outcome events

The primary end-point was the incidence of symptomatic recurrent venous thromboembolism demonstrated by objective tests. All patients who became symptomatic for recurrent DVT during the follow-up were asked to return immediately to undergo repeat ultrasonography. Ultrasonographic findings were categorized as positive for DVT recurrence if a previously normal(ized) vein had become non-compressible, if a new segment had become non-compressible, or if the residual vein diameter in either venous segment had enlarged (0.2 mm) compared with the previous assessment.[18] The occurrence of PE was demonstrated by a high probability ventilation-perfusion scintigram or by abnormal pulmonary angiography.

Secondary end-points were major hemorrhage, defined as a decrease of at least 2.0 g/dL in the hemoglobin concentration, the need for transfusion of two or more units of blood, an intracranial, retroperitoneal, or intra-ocular bleed, and death. All outcome events were assessed during the initial treatment period and during the 3 months of follow-up. Each recurrent venous thromboembolic and bleeding event, as well as all deaths, were assessed by an independent adjudication committee consisting of two physicians; disagreements were resolved by a third physician.

Statistical analysis

Based on historical controls and data from the literature we considered *a priori* that a frequency of venous thromboembolic events of 4% or less with an upper 95% confidence limit of 7% would be clinically acceptable. Ninety-five percent confidence intervals (95% CI) were calculated with the normal approximation to binomial distribution.

Results

Study patients

During the observation period between March 1997 and March 2002, DVT was diagnosed by compression ultrasonography in 309 patients. In nine patients DVT was confirmed after a repeat ultrasonography. Fifteen patients (4.9%) could not be treated with LMWH on an outpatient basis. Ten of these patients had a clinical suspicion of PE, which was confirmed by high probability ventilation-perfusion scintigraphy in five. Three patients were ineligible for outpatient treatment because of the need for hospitalization (disseminated bladder cancer, disseminated prostate cancer, high fever, idiopathic platelet function abnormality and leukopenia). Finally, one patient was pregnant (32 weeks), and one was a nursing home patient. A total of 294 consecutive patients (95%), of whom 135 were male (mean age 58 years; standard deviation [SD] 16 years) and 159 were female (mean age 55 years, SD 20 years), were treated according to protocol on a full outpatient basis with nadroparin followed by acenocoumarol. Proximal DVT was demonstrated by compression ultrasonography in 238 patients (81%), isolated distal DVT was detected in 51 patients (17 %), while five patients had thrombosis of the upper extremity (2%). The clinical characteristics of the patients are shown in Table 1. At presentation, 57 (19%) patients had a medical history of venous thromboembolism, and 37 (13%) patients were suffering from a malignancy.

Treatment and follow-up

Nadroparin, 9,500 IU anti Xa/mL, was given to 145 patients twice daily while 149 patients received once daily nadroparin, 19,000 anti Xa/mL. There were no marked differences in clinical characteristics between the patients receiving nadroparin twice daily and those

Table 2. Complications of outpatient nadroparin treatment during the initial LMWH treatment and during the 3 months of follow up (n=294).

Age at presentation (yr.)	*Day of recurrent DVT (INR*)*	*Day of PE (INR*)*	*Diagnosis[1]*	*Day of MB (INR*)*	*Days to achieve therapeutic INR**	*Bleeding site, action*	*Death (days)*	*Cause of death*	*Co-morbidity*
54	11 (2.9)		CUS		5		60	Disseminated colon cancer	
47	15 (4.0)		CUS		4		64	Disseminated lung cancer	
91					3		42	Possible disseminated prostate carcinoma	NIDDM, admission due to hypoglycemic coma
54	77(2.8)		CUS		5				
60	42 (3.1)		CUS		4				Disseminated bladder cancer
86				Treated with LMWH only			84	Hepatic metastasis, unknown primary	
65	88 (1.6)		CUS		4				
52		1(4.6)	V/P scan		4				CABG
36		7 (1.7)			6				
68				68 (>10)	3	Gastrointestinal bleeding, treatment cessation, prothrombin complex			Disseminated colon cancer
78				14 (3.4)	4	Macroscopic hematuria, 4 PC	31	Bladder carcinoma (T4N2Mx)	
80				39 (7.3)	5	Gastrointestinal bleeding, treatment cessation, PC			
60					6		64	Disseminated pancreatic cancer	
83					5		60	No clinical evidence of PE or MB	
78					3		34	Melanoma, brain metastasis and cachexia	Disseminated lung cancer
72					3		51	Disseminated endometrial cancer	
36				3 (>10)	3	Gastrointestinal bleeding	36	Renal function disorders, no dialysis	Dementia , CVA, right sided paralysis, NIDDM, polymyalgia rheumatica
69	14 (3.2)	27 (2.5)	CUS		4				Disseminated lung cancer
	6 (2%)	3 (1%))		4 (14%)			10 (3.4%)		PE, pneumonia, DVT both legs

*:denotes INR on the day of the complication or the closest day. DVT: deep vein thrombosis; PE: pulmonary embolism; Dx: method used to confirm diagnosis; MB: major bleeding complication; CUS: compression ultrasonography; V/P scan: ventilation/Perfusion scintigraphy; PC: blood transfusion of erythrocyte concentrate.

receiving the once daily injections, except for thrombus localization (Table 1). The subcutaneous LMWH injections in our patients were administered the general practitioner's office, which was feasible in all patients throughout the study. Patients were treated with LMWH for a mean of 5.4 days (range 2-84 days, SD 6.7 days). The mean duration of acenocoumarol treatment was 3 months (SD 1.6 months). Twenty-four complications (8.2%) occurred in 18 patients during the 3-month follow-up period. Recurrent venous thromboembolism, major hemorrhage and death occurred in 3.1%, 1.4% and 3.4% of the patients, respectively (Table 2).

Recurrent venous thromboembolism

Nine patients suffered a recurrent venous thromboembolism (3.1%; 95% confidence interval [CI] 1.1 to 5.0). Six patients experienced a recurrent DVT, as demonstrated by compression ultrasonography, on day 11, 14, 15, 42, 77, and 88. DVT was localized in the contralateral leg in four of them, one patient suffered from a recurrent DVT of the subclavian vein after 14 days and in one patient DVT recurred in the ipsilateral leg after 77 days. All recurrences occurred after nadroparin treatment had been stopped. Four of these six patients had been treated with once daily nadroparin injections (Table 3). In all six patients the initial diagnosis of DVT

Table 3. Complications of once versus twice daily nadroparin treatment and day of occurrence (n=294).

Complication	*Once daily N. (day) n= 149*	*Twice daily N. (day) n= 145*	*Total*	*OR*	*95% CI*
Pulmonary embolism	3 (1,7,27)	0	3		
Days 0-10	2	0			
Days 10-90	1	0			
Recurrent DVT	4 (42,44,77,88)	2 (11,15)	6	2,0	0,4-11
Days 0-10	0	0			
Days 10-90	4	2			
Venous thromboembolism	7	2	9	3.5	0.7-17
Days 0-10	2	0			
Days 10-90	5	2			
Major bleeding complication	4 (3,14,39,68,)	0	4		
Days 0-10	1	0			
Days 10-90	3	0			
Death	7 (31, 34.36,51, 60,64, 84)	3 (42, 60,64)	10	2.3	0.6-9.2
Days 0-10	0	0			
Days 10-90	7	3			

had been established on the first day of presentation.

A clinically suspected PE occurred in three patients. During the initial treatment period, one patient, in whom DVT had occurred 6 days after a coronary artery bypass graft operation, had to be hospitalized 24 hours after starting LWMH treatment because of suspected PE, which was confirmed by a high probability ventilation-perfusion scan. The LMWH was continued and oral anticoagulant treatment was administered with the aim of maintaining the INR at a higher level of between 3.0 and 4.0. After the initial treatment period suspected PE occurred in two more patients on day 7 and 27; both patients had been treated with once daily nadroparin injections. In the first patient PE occurred during the second week of anticoagulant treatment. No additional diagnostic tests were performed to confirm the diagnosis of PE, since the attending physician concluded that the results of such tests would have no consequences for the treatment. Oral anticoagulant treatment was continued for 3 months without any complications. The second patient had a medical history of disseminated lung cancer and was admitted to hospital. Because of the patient's poor clinical condition no further tests were performed to confirm the diagnosis of PE. At follow-up this patient suffered from DVT of the subclavian vein on day 44 and had to be readmitted on day 99 after further deterioration of the clinical condition; the patient died 9 days after readmission. Autopsy demonstrated metastatic lung cancer as well as pulmonary embolism and lung infarction.

Major hemorrhage

A non-fatal major bleeding complication occurred in four patients (1.4% 95% CI: 0.04 to 2.7); all had been treated with once daily nadroparin injections. Three of the four major bleedings occurred during acenocoumarol treatment. One patient had to be hospitalized after 14 days of treatment because of gross hematuria due to bladder cancer (T4N2Mx) (INR 3.4) requiring instant radiation therapy. This patient died on day 31 from metastatic disease. The second patient was admitted to hospital on day 39 with bleeding from the upper gastrointestinal tract (INR 5.3), which required a blood transfusion. The third patient was hospitalized on day 68 because of severe gastroenteritis and a gastrointestinal bleed (caused by esophagitis) (INR > 10), which was successfully treated with prothrombin complex (Cofact®). The fourth patient suffered from gastrointestinal bleeding after 3 days of nadroparin treatment and required blood transfusion.

Deaths

Ten patients died (3.4% 95% CI 1.3 to 5.5); seven of these patients had initially been treated with once daily nadroparin injections. Eight died because of disseminated malignancy, of whom three had to be hospitalized for various reasons. One patient died because of advanced renal failure for which further therapy was refused. In another patient the cause of death remained unclear; however there was no clinical evidence that pulmonary embolism or major hemorrhage had occurred.

Discussion

In this prospective study we validated a protocol of home anticoagulation in a large cohort of unselected patients in daily routine practice. In contrast to other protocols we had a low threshold to include patients because we had few predefined reasons for exclusion. Furthermore patients went to their general practitioners to receive the LMWH injections. These measures allowed us to treat more than 95% of all patients with DVT in a full out of hospital setting. The rate of recurrent venous thromboembolism rate was 3.1%, one patient returning after 1 day with PE. The rate of major bleeding was 1.4% (four patients), with two patients developing a major bleeding complication in the first 2 weeks. Importantly no patient died as a result of fatal PE or of major hemorrhage. The complications rates observed in our study compare well with the rates observed in two large clinical trials in selected outpatients as well as in more recent cohort studies. In these studies the rate of major hemorrhage ranged from 0 to 2%, that of recurrent venous thromboembolism from 3 to 9%, and that of death from 5 to 9%.[8-10,13-16]

Patients with DVT and known malignancy are often considered to be a distinct patient population because they have a higher risk of both recurrent DVT and bleeding complications during anticoagulant therapy. Until recently, patients with active cancer were often excluded from outpatient treatment studies. In a recent study[19] 22 patients with a malignancy out of 72 patients were treated on an outpatient basis and it was concluded that a known malignancy does not exclude the possibility of home treatment. Within our study cohort 37 patients with a known malignancy were treated on an outpatient basis; five patients had to be admitted to hospital for various reasons, including severe gastroenteritis, necrosis of feet, hypoglycemia, recurrent thrombosis and deterioration of clinical condition. Four of the six patients in whom recurrent DVT occurred had active cancer, underscoring the high risk of recurrent venous thromboembolism in these patients. Indeed, in a prospective follow-up study Prandoni *et al*.[20] demonstrated that patients with cancer are more likely to develop recurrent thrombo-embolic complications and major bleeding during anticoagulant treatment. It was concluded in that study that the higher incidence of complications could not be explained by either subtherapeutic anticoagulation or or over-anticoagulation, but was more likely due to disease progression and immobilization. Recent studies demonstrate the superior efficacy of LMWH treatment over vitamin K antagonists in patients with cancer;[21-23] however, at the time our study was designed, neither these two studies nor the latest ACCP guidelines had been published.

There are several issues of this study worth commenting. First, there was a non-significant trend for an increased rate of recurrent venous thromboembolism in the patients treated with nadroparin once daily (OR 3.5; 95% CI 0.7-17). Although we realize that these findings are derived from a non-randomized population and should be considered a *post-hoc* analysis, they are in line with results of a recent review.[24] In this review, it was concluded that although once daily treatment with LMWH is as effective and safe as twice daily treatment with LMWH, the obtained 95% confidence interval implied that there is a possibility that the risk of recurrent venous thromboembolism might be higher when patients are treated once daily. We think that our results should alert clinicians to base their decision on whether to treat a patient with a once daily regimen on a choice between increased convenience and the potential for a lower efficacy of the once daily LWMH regimen. Second, in our healthcare setting it is possible to treat patients with LMWH injections in the general practitioner's office; this may limit the external validity of our findings in other countries where this may not be possible. However, Wells *et al*. showed that outpatient treatment in Canada is feasible provided an established outpatient treatment management model is used.[16]

Beyond the observation that our protocol of outpatient treatment of DVT is effective and safe, it can also assumed to be cost saving, on the basis of a reduced need for hospitalization. It is well known that intravenous heparinization requires 7 to10 days of hospitalization. Recently, it was demonstrated that this intravenous heparin treatment *per se* delays discharge for a median of 3 days in more than 60% of patients.[25,26] Furthermore, home treatment is well accepted by all patients and has been shown to be associated with high patient satisfaction.[8,9,26] It is worth noting that a multidisciplinary medical team with experience in the management of venous thromboembolism is required to implement the outpatient treatment protocol successfully.[27]

We conclude that our simple protocol for LMWH outpatient treatment of DVT has great potential for daily clinical practice since it is feasible in nearly all patients with DVT referred to emergency departments of non-academic hospitals. The results of our study will facilitate the clinical decision making process of clinicians considering outpatient treatment of DVT in such a setting.

MZ: conception and design of the study, acquisition, analysis and interpretation of data, drafting the article, final approval of the version to be published; LHvH, BJB: substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data, revising the manuscript critically for important intellectual content; and final approval of the version to be published; MVH: substantial contributions to the conception and design of the study or acquisition of data, or analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published.

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