Clinical Outcome and Cost of Hospital vs Home Treatment of Proximal Deep Vein Thrombosis With a Low-Molecular-Weight Heparin

The Vascular Midi-Pyrenees Study

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Background: Low-molecular-weight heparins have been shown to be effective and safe in the treatment of deep vein thrombosis. To our knowledge, there have been no direct comparisons of such treatment on an outpatient vs an inpatient basis.

Objective: To conduct a randomized, comparative, multicenter trial to evaluate the clinical outcomes and treatment costs of deep vein thrombosis in the outpatient and inpatient settings.

Methods: Two hundred one patients presenting with proximal deep vein thrombosis, without known risk factors for pulmonary embolism or hemorrhagic complications, were randomized to receive a low-molecular-weight heparin at the registered dose followed by an oral anticoagulant for up to 6 months, either in the hospital for the first 10 days followed by treatment at home (n=102) or at home from the outset (n=99). The primary clinical outcome was the incidence of venous thromboembolism recurrence, pulmonary embolism, or major bleeding. The economic analysis was performed from the point of view of the health insurance company. Total costs of the 2 management strategies were calculated to compare the cost consequences during the first 10 days.

Results: No differences in clinical outcome were detectable between the 2 groups. There was no increase in the rates of primary efficacy outcome in the patients treated at home vs in the hospital (3.0% vs 3.9%), while a cost reduction of 56% was demonstrated for outpatient management.

Conclusion: For patients with proximal deep vein thrombosis and no symptoms of pulmonary embolism or increased risk of major bleeding, home treatment using a low-molecular-weight heparin is an effective, safe, and cost-saving strategy.

Arch Intern Med. 2000;160:1769-1773

DEEP VEIN thrombosis (DVT), a disease with an estimated annual incidence of 1.6 per 1000,1 is a significant source of morbidity and mortality, and its management incurs considerable health care costs. For the past 30 years, the standard treatment for patients with acute DVT has been the immediate administration of continuous intravenous heparin, followed by long-term therapy with an oral anticoagulant to prevent further thrombosis propagation or embolism. Because of the need to monitor the effect of unfractionated intravenous heparin, hospitalization has been necessary. Recently, several studies2-4 have confirmed that a low-molecular-weight heparin (LMWH), produced by enzymatic or chemical hydrolysis of conventional heparin, given subcutaneously twice a day is at least as efficacious as continuous intravenous or subcutaneous unfractionated heparin in preventing recurrence of thrombosis, death, or major hemorrhage and is also associated with a lower incidence of thrombocytopenia.5 Low-molecular-weight heparins have some advantages over standard unfractionated heparin,6 including better bioavailability and longer plasma half-life7 and a better efficacy-safety ratio.8 The reduced variability in the anticoagulant response of LMWH9 means it can be administered at a dosage adjusted for body weight, without the need for continuous laboratory monitoring, opening up the possibility of outpatient (home) treatment for proximal DVT.

Proximal DVT is routinely initially treated with an LMWH given by subcutaneous injection, which can be delivered at home. There have been some recent randomized studies10,11 in which this treatment strategy has been reported to be as efficacious and safe as the intravenous administration of unfractionated heparin in the hospital. The cost consequences of...
PATIENTS AND METHODS

PATIENTS

Male and female patients, between the ages of 18 and 85 years, with clinical symptoms and a confirmed diagnosis of proximal DVT dating from not more than 30 days before enrollment were eligible for inclusion. The diagnosis of DVT in the popliteal, femoral, and iliac veins was documented by ultrasonography or by venography. Patients were excluded if they had a thrombus located in the inferior vena cava, a floating thrombus, a history of DVT within the preceding 6 months, DVT with an objectively documented symptomatic pulmonary embolism, a clinical context needing hospitalization, or a contraindication to anticoagulant treatment (short- or long-term anticoagulants); if they received treatment with heparin (other than prophylactic) within the 48 hours preceding inclusion; if they were pregnant; if home treatment or a hospital stay was impossible; if they lived too far from the center; or if they would not give written consent. Patients were examined for risk factors for DVT, including previous thromboembolism, varicose veins, immobilization, surgery, trauma, cancer, use of oral contraceptives, or known inherited or acquired clotting disorders, and for other comorbidities (eg, cardiovascular disease with right ventricular failure).

STUDY DESIGN

The clinical study was a randomized, comparative trial involving 17 hospital centers. The study was performed in accordance with the revised Declaration of Helsinki and Good Clinical Practice, and was approved by the relevant institutional review boards. The study was approved by the local ethical committee on May 6, 1993. Private angiologists, general practitioners, and nurses participated in collaboration with the local hospital. All eligible patients presenting to the participating centers were asked if they would be willing to be enrolled in the trial. On referral to the hospital with suspected DVT, patients underwent either duplex ultrasonography or venography, according to the standard practice at the center concerned, to confirm the diagnosis. Patients who proved eligible and who gave their written, informed consent were randomized, using sealed forms, to receive either immediate home treatment under the care of their general practitioner and a nurse, or hospital care for the duration of the initiation of oral anticoagulant treatment (ie, for 10 ± 2 days) followed by home treatment as with the first group.

Both groups received the same treatment with an LMWH at the recommended dose given by subcutaneous injection. The attending physician was free to choose an LMWH from among those registered and marketed in France for this indication. The LMWH regimens used did not differ significantly from those approved in other countries, including the United States, for the treatment of DVT. However, not all the LMWHs chosen by the attending physicians in this study were approved in France for the treatment of established DVT. All patients also received an oral anticoagulant (anti–vitamin K or fluindione, 20 mg/d) for the first 3 days, followed by a regimen designed to maintain the international normalized ratio between 2 and 3, for a treatment period of up to 6 months. Under the supervision of the general practitioner and a nurse, patients were also given compression stockings for up to 6 months and were encouraged to return to physical activity according to an approved schedule.

ASSESSMENT OF THE CLINICAL OUTCOME

The primary end point for assessment of the clinical outcome was the incidence of DVT recurrence, pulmonary embolism, or major bleeding. Recurrence of DVT was defined as the progression of thrombus into a venous segment not initially involved, rethrombosis in the same segment of vein that had previously been thrombosed and repermeabilized, or both. All patients were systematically examined by duplex ultrasonography on days 10 (± 2 days), 30 (± 5 days), 90 (± 5 days), and 180 (± 5 days). Clinical suspicion of DVT recurrence was confirmed by ultrasonography, venography, or both. The diagnosis of pulmonary embolism was documented by ventilation perfusion scan and, if necessary, by angiography. Major bleeding was defined as bleeding events associated with a decrease in hemoglobin concentration of at least 20 g/L or a hemorrhage requiring a transfusion of 2 U of blood or placing a major organ or tissue at risk. Patients who experienced recurrence of DVT were also given compression stockings for up to 6 months and were encouraged to return to physical activity according to an approved schedule.

RESULTS

A total of 204 patients was enrolled in the study between September 2, 1993, and March 28, 1997. Internal studies to evaluate the rate of enrollment estimated the proportion of screened patients considered eligible and who gave informed consent at 11.8%. Two subjects were wrongly enrolled (one presenting with a pulmonary embolism and the other with hepatic insufficiency), while a third patient declined to participate any further after having given informed consent and being randomized. Of the remaining 201 patients, 99 (49.3%) were randomized to outpatient treatment at home and 102 (50.7%) to hospitalization.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics of the 2 treatment groups were comparable (Table 1). Of the 201 patients enrolled, 82 (40.8%) had at least 1 comorbidity, for which 77 (38.3%) required associated treatment. The pres-
venous thrombosis, pulmonary embolism, or major bleeding were withdrawn from the trial, and their treatment was adapted accordingly. Mortality was assessed as due to a pulmonary embolism, a hemorrhagic complication, or another cause. Minor bleeding was used as a secondary end point for the assessment of safety.

ECONOMIC ANALYSIS

An economic analysis was performed in parallel with the clinical study to compare the cost impact of outpatient vs hospital treatment. For both treatment groups, the cost of treatment of complications, such as hemorrhage, was excluded from the evaluation. The cost consequences of replacing inpatient care with outpatient care were assessed only during the first 10-day period, since the treatments did not differ appreciably thereafter. Only direct medical costs were taken into account, since nonmedical costs such as transport costs were not systematically documented. Indirect costs (loss of earnings) were considered negligible as the mean age of the patients was high (64 years). Data on resource use were available for 94 outpatients and 98 inpatients. The economic analysis was performed from the point of view of the health insurance company.

The number of days of treatment, the number of nursing visits, and the number of biochemical analyses were collected prospectively and were available for all outpatients. The number of duplex ultrasonographic scans and physician visits was collected for a sample of 45 outpatients only, to calculate an average that was then applied to all outpatients.

The elements taken into account in the economic calculations were as follows:

1. Outpatients. The cost of treatment with an LMWH, calculated as the average price of 2 subcutaneous injections (Fr 122.40 per day) multiplied by the number of days of treatment; the cost of nursing visits, calculated as 2 visits at Fr 16.50 per day, ie, Fr 33 per day, multiplied by the number of days of treatment with an LMWH; the cost of the duplex ultrasonographic scans (2 on average), estimated to total Fr 756; the cost of biochemical analyses, similarly estimated to total Fr 648; and the cost of visits (general practitioner or specialist), 2 on average, totaled Fr 220. This figure was applied to all 99 patients in the calculation.

2. Inpatients. The calculation for patients treated in the hospital differed according to whether the hospital was public or private. For private hospitals, costs were calculated from reimbursement rates according to the health insurance guidelines. The average cost for a hospital day (Fr 506.10) was multiplied by the number of days of hospitalization for each patient and by adding the costs of duplex ultrasonography and biochemical analysis as for the outpatients and of 1 to 2 visits by the attending physician at Fr 150 each. Most inpatients (n=92) attended public nonprofit hospitals. Here, the calculations were based on the “groupes homogenes de malades,” the French adaptation of the US diagnosis-related groups, and the corresponding “indice synthetique d’activite points,” which are based on actual costs. The chosen reference point was that of the Midi-Pyrenees in 1996, Fr 14.74. The calculation was based on the length of hospital stay of each patient. If the stay was longer than 1 hospital day, the groupes homogenes de malades was considered to be 185 (deep venous thrombosis), which represented 1646 indice synthetique d’activite points (Fr 24262). For patients with a hospital stay equivalent to 1 day, the groupes homogenes de malades was considered to be 805 (cardiovascular outpatient without surgery), representing 277 indice synthetique d’activite points or Fr 4083.

STATISTICAL ANALYSIS

The sample size was based on an estimated rate of complications (thromboembolic recurrence or major bleeding) of 13% among the hospitalized group. To detect an increase to 25% among the group treated entirely at home, with a 1-sided error of 5% and a power of 85%, 248 patients per treatment were withdrawn from the trial, and their treatment was adapted accordingly. Mortality was assessed as due to a pulmonary embolism, a hemorrhagic complication, or another cause. Minor bleeding was used as a secondary end point for the assessment of safety.

Physicians had free choice of which registered LMWH to prescribe. Nadroparin calcium was administered to 44.5% of the patients, enoxaparin sodium to 39.0%, and dalteparin sodium to 16.5% (Table 2). On average, treatment with an LMWH lasted a mean±SD of 8.6±5.2 days, with no significant (P=.71) difference between the 2 treatment groups. At the point when LMWH treatment was discontinued, 52.9% of all patients had an international normalized ratio within the recommended limits. In 28.6% of the patients, it was above 3; in 18.5%, below 2. The slight trend toward a better international normalized ratio in the hospitalized patients did not reach statistical significance.

Most patients (73 [74%] of 99) randomized to the outpatient arm either were not hospitalized at all or were inpatients for less than 24 hours; however, a few required hospitalizations of 2 days or more. Conversely, most patients in the hospitalization group were inpa-
patients for at least 48 hours; however, 10% were hospitalized for shorter periods (Table 3).

Of the 201 patients, 38 (18.9%) did not complete 6 months of follow-up. Premature withdrawal was twice as frequent in the hospitalization arm, and the most common reason given was the patient’s own wish. Seven patients, 4 in the hospitalization arm and 3 in the outpatient treatment group, withdrew due to severe complications (3 DVT extensions and 4 major hemorrhages).

### CLINICAL OUTCOMES

Three patients (1 outpatient and 2 inpatients) developed thrombus extensions. Severe hemorrhage was experienced by 2 patients in the outpatient group (1 gastrointestinal tract hemorrhage on day 12 and 1 recurrent hemorrhrosis) and 2 inpatients (hemoptysis on day 13 and at 2 months). All but 1 of these patients had associated risk factors, including previous DVT and a history of pulmonary neoplasia.

Two patients died during the study. Both of these patients were hospitalized, and the deaths (one due to the occurrence of acute phase of chronic lymphocytic leukemia, the other due to cerebral metastasis of a mammary tumor) were considered related to the treatment.

Twenty-eight patients (11 inpatients and 17 outpatients) experienced minor bleeding. Most of these events occurred before day 10. There was no significant ($P<.20$) difference in incidence between the 2 groups.

### ECONOMIC RESULTS

As the clinical results for efficacy and safety were similar between the 2 treatment groups, a cost minimization analysis was performed. The mean±SD cost of outpatient treatment for the initial 10-day period was Fr 9230±2005, compared with Fr 20932±1482 for inpatient treatment, which is 2.25 times higher. Thus, outpatient management showed a cost reduction of 56%.

Preferential clinical trials have indicated that treatment of patients with DVT using a fixed-dose LMWH is at least as safe and effective as the conventional management with unfractionated intravenous heparin. In principle, this simplified treatment can be offered on an outpatient basis, thus reducing patient inconvenience and health care costs. Two previous trials have indicated that outpatient management of DVT is effective and safe. For one of these studies, a cost comparison was published that indicated that outpatient treatment of DVT reduces resource use and total treatment cost.

However, these trials have compared 2 different heparin treatment regimens (LMWH and unfractionated heparin) in the 2 different settings (outpatient and inpatient, respectively). In this study, we therefore aimed to compare inpatient with outpatient care directly, using the same treatment modality with an LMWH.

One question concerning the analysis of the results is the small proportion of screened patients who were enrolled in the study. During the trial, 2 internal analyses were therefore carried out to investigate the reasons for noninclusion during the 2 periods, March to June 1994 (n = 148) and October to December 1994 (n = 90). By far, the most common reason (47.3% in the spring and 60.0% in the autumn) for noninclusion in the trial of a patient presenting with DVT was that the patient was hospitalized for another reason. These patients were excluded because their inclusion would have affected the distribution of patients to outpatient vs inpatient care. Thus, the rigor of the inclusion criteria is reflected in the number
of patients rendered noneligible for the purposes of this study.

The results confirm those of previous studies, demonstrating that the 2 treatments are equivalent for their efficacy and overall safety. The number of patients enrolled was not large enough to detect a small difference between treatment groups in the number of pulmonary embolisms. However, given the other available clinical data and the lack of difference in other clinical outcomes observed in the trial, there is no a priori reason to suspect such a difference. The results suggest that home treatment with an LMWH for DVT can be recommended if there is no clinical suspicion of a pulmonary embolism or a bleeding complication and if the patient has no known hemostatic disorder. In practice, there will be other nonclinical reasons to contraindicate outpatient treatment for DVT, eg, if administration of injections or regular domiciliary care cannot be guaranteed. Nevertheless, it is anticipated that most patients will prefer home treatment because it reduces the disruption of their normal lives. Harrison et al reported that 91% of their patients preferred being treated at home using self-injection.

Risk factors and comorbidities were higher in home-treated patients. A subgroup analysis of this difference has not been carried out. However, any potential bias derived from this difference would be expected to decrease the overall efficacy and safety of home treatment. The fact that this is not observed is further support for the equivalent efficacy and safety of the 2 treatments.

An important aspect of our study was the cost comparison of the 2 treatments, which showed a clear advantage of home treatment over hospitalization for cost minimization. Some caveats should be mentioned. For example, the cost of the treatment of complications was excluded from the analysis because of inadequate documentation. Since, however, no difference in complication rate between the 2 treatments was noted, it is unlikely that inclusion of this factor would substantially affect the conclusion that outpatient treatment is a cost-saving strategy. The study indicates that an effective strategy would be a combination of the 2 treatments, in which a 1-day hospitalization would be followed by outpatient care.

Accepted for publication May 23, 1999.

This study was supported by a grant from the French National Ministry of Health (Programme Hospitalier de Recherche Clinique, 1993); Sanofi, Gentilly, France; and Rhone-Poulenc Rorer, Strasbourg, France.

We thank Anne Dumoulin, MD, for help with the data analysis; Alain Grand, PhD, MD, and Jacques Pous, MD, for their help with the methods and collection and analysis of the data; Jackie Leach Scully, PhD, for contributing to the planning and final version of the manuscript; and Marie-Odile Carrere, PhD, for her advice on the economic evaluation.

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