Reduction in Thrombus Extension and Clinical End Points in Patients after Initial Treatment for Deep Vein Thrombosis with the Fixed-Dose Body Weight-Independent Low-Molecular-Weight Heparin Certoparin

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ABSTRACT

Low-molecular-weight heparin (LMWH) is effective in the treatment of acute deep vein thrombosis (DVT). This has not been demonstrated for one LMWH alone. The relationship between venographic changes due to LMWH therapy and clinical outcome in the initial treatment period has not been reported. A pooled analysis of two clinical trials was performed. The trials compared a fixed-dose, body weight-independent, subcutaneous LMWH, certoparin (8000 aXa [aXa] U twice a day [b.i.d.]), with an adjusted-dose intravenous unfractionated heparin (UFH) with respect to venographic changes expressed as Marder score and occurrence of recurrent venous thromboembolism, major bleeding, and mortality. The Marder score was 23.2 ± 8.4 in patients randomized to LMWH (n = 299 paired phlebograms) and 23.9 ± 8.9 in patients allocated to UFH (n = 297 paired phlebograms) at entry (2p = 0.23) and 18.9 ± 9.7 and 20.5 ± 9.9 at the end of the initial therapy (2p = 0.04), respectively. The composite outcome of recurrent venous thromboembolism, major bleeding, and mortality occurred less frequently during treatment with LMWH (n = 393) than it did with UFH (n = 404, 1.3% versus 5.0%, risk reduction [RR] 0.26, 95% confidence interval [CI] 0.11 to 0.63, 2p = 0.004). Single events of recurrent thromboembolism (2p = 0.12), major bleeding (2p = 0.03), and mortality (2p = 0.12) were observed less frequently with LMWH. A trend toward a lack of regression of thrombus size was observed in recurrent venous thromboembolism (2p = 0.08). Body weight–independent LMWH significantly reduces thrombus size and the incidence of composite outcome during the initial treatment of acute proximal venous thrombosis compared with adjusted dose intravenous UFH. A definite conclusion of a relation between an unimproved Marder score and a recurrent venous thromboembolism requires confirmation.
KEYWORDS: Deep vein thrombosis, low-molecular-weight heparin, Marder score, composite outcome, bleeding complication

Objectives: Upon completion of this article, the reader should be able to (1) list the design features of the described clinical trial and (2) describe the outcome of the trial.

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UFH has been the standard anticoagulant for initial treatment of DVT for many decades. Bleeding complications, heparin-induced thrombocytopenia, and the necessity of monitoring have resulted in a focus on the limitations and shortening of treatment of acute DVT and on the development of LMWHs. The improved pharmacological properties of LMWHs include higher aXa activity compared with anti-factor IIa activity, less binding to plasma proteins, prolongation of half-life, high relative bioavailability after subcutaneous administration, and predictable anticoagulant responses have prompted an improvement in the treatment of venous thromboembolism. Body weight-adjusted dosages have been developed to increase the predictable anticoagulant response and to avoid drug monitoring. A summary of clinical studies demonstrated a significantly greater reduction of the Marder score comparing the first venography at entry with the second at the end of the initial treatment in favor of LMWH.

Further meta-analyses demonstrated a reduced occurrence of recurrent venous thromboembolism and of mortality 3 to 6 months after initial treatment with LMWHs compared with UFH. These results differ from individual studies in which the different LMWHs were investigated. Consequently, most of the clinical studies have aimed at demonstrating an equivalence in the outcomes of treatment with UFH. Another meta-analysis concluded that LMWHs are at least as effective as UFH in preventing recurrent venous thromboembolism (VTE) but that it is unlikely that LMWHs are superior despite a statistically significant decrease in total mortality. However, pooling of data from clinical studies may present difficulties, such as homogeneity of patients and of LMWHs.

Two pilot studies indicated the efficacy and safety of intravenous LMWH certoparin for the treatment regimen of acute DVT. Two multicenter studies have demonstrated the efficacy and safety of this therapy. In each of these two trials, the reduction of the Marder score showed a nonsignificant trend in favor of LMWH at the end of the initial treatment. In one of these trials, the composite outcome of recurrent VTE, mortality, and major bleeding complications was lower during treatment with LMWH compared with UFH after the initial treatment and was maintained for at least 6 months.

The first objective of the present analysis was the question of the efficacy and safety of one LMWH based on the Marder score from repeated ascending venography at the beginning and end of the initial treatment and of the composite outcome of recurrent thromboembolism, mortality, and major bleeding. The design of the two studies and the biographical data of the patients were similar, prompting us to analyze the results of the Marder score together in order to evaluate the efficacy of the fixed-dose, body weight-independent dosage of a single LMWH compared with UFH. We also investigated the relation of the changes of the Marder score to the clinical outcome of thromboembolism. Furthermore, after the initial heparin therapy, we analyzed the occurrence of recurrent VTE in relation to a lack of thrombus regression, judged from paired phlebographies.

METHODS

Study Design

The two studies were multicenter, randomized, European clinical trials comparing fixed-dose body weight–independent subcutaneous LMWH (certoparin) with activated partial thromboplastin time (aPTT)–controlled intravenous UFH in patients with acute proximal DVT. In the participating countries, treatment is routinely performed with dose-adjusted intravenous UFH in hospitalized patients. Patients ≥30 years of age with acute symptomatic proximal DVT (i.e., thrombosis in the popliteal or more proximal vein) documented by ascending venography according Rabinov and Paulin were eligible. Patients were excluded from the study if they had one of the following: indication for surgical or fibrinolytic treatment of DVT, duration of symptoms for more than 3 weeks, ongoing oral anticoagulation, renal failure, severe hypertension (blood pres-
sure >200 mmHg systolic and >105 mmHg diastolic while on antihypertensive treatment), severe hepatic failure, currently active bleeding or disorders contraindicating anticoagulant therapy, contraindication to oral anticoagulants, pregnancy, known intolerance to heparins, intolerance to contrast media, any surgery within the past 8 days, acute severe pulmonary embolism, platelet count <100 \times 10^9/l, treatment with heparin >24 hours before inclusion into the study, and treatment with platelet-inhibiting drugs.

**Treatment Regimes**

Patients were randomly assigned to therapy with LMWH or UFH for 12 days. They received a fixed dose of 8000 aXa certoparin (Mono-Embolex® NM, Novartis Pharma, Nuremberg, Germany) b.i.d. subcutaneously or UFH with an initial bolus of 5000 IU followed by a continuous intravenous infusion at an initial rate of 20 IU/kg per hour. The dose of UFH was subsequently adjusted to a target aPTT of two to three times the reference value. The aPTT tests were performed 4 to 6 hours after the start of treatment and thereafter once daily. If a subtherapeutic coagulation time was determined, the dose was adjusted and the aPTT repeated within 6 hours.

Oral anticoagulation (vitamin K antagonists) was started before day 10 and was continued for up to 6 months. Treatment with LMWH or UFH was stopped as soon as the international normalized ratio (INR) was above 2.0 for 2 consecutive days.

**Primary Outcome Measure**

Patients underwent a second ascending venography of the affected leg between days 7 and 15 unless clinical symptoms prompted an earlier test. Venographies were evaluated by two independent radiologists who were unaware of the treatment of the patients and of the chronological order of venographies. The thrombosed veins were assessed quantitatively according to the scoring system of Marder et al.21 In the original studies, the primary outcome measure was defined as a relevant reduction of the Marder score of ≥30% on the second venography, as compared with the one obtained at entry. In the present analysis, the absolute values of the Marder score were used for the statistical analysis because of the low number of patients with a 30% or more thrombus progression in the second phlebography, compared with that at entry.

**Composite Outcome**

The secondary outcome measure of the study was the composite outcome of recurrent VTE, major bleeding, and death during the initial treatment period. An independent adjudication committee that was unaware of the treatment assignment evaluated data on all potential outcome events. The three outcome measures of the composite end point were also evaluated separately. Signs and symptoms of recurrent VTE or hemorrhage were carefully recorded. Patients with suspected recurrent DVT underwent ascending venography. Patients in whom pulmonary embolism was clinically suspected underwent ventilation-perfusion scanning. Pulmonary embolism was diagnosed when a high-probability perfusion defect was documented or when documented by pulmonary angiography. In case of death, autopsy was performed whenever permission was obtained. Bleeding was defined as major if it was overt and either it was associated with a decrease in the hemoglobin concentration of at least 2g/dl; a transfusion of more than 2 units of blood was indicated; or the bleeding was intracranial, retroperitoneal, or intraspinal.

**Marder Score and Recurrent Venous Thromboembolism**

The incidence of recurrent venous thromboembolism was analyzed in patients with paired phlebographies. The phlebographic results were divided into the categories of no improvement and improvement of the Marder score in the second venography compared with that at entry of treatment.

**Statistical Methods**

The analysis of the Marder score at the first and second phlebography was performed using Wilcoxon’s rank test; analysis of the relation between recurrent VTE and the Marder score was performed using Fisher’s exact test.

**RESULTS**

**Patients and treatments**

Of the 797 patients, 393 were randomized to LMWH and 404 to UFH. No differences in the baseline characteristics of the two treatment groups could be detected (Table 1). The dosage of LMWH was 8000 aXa IU b.i.d. subcutaneously throughout the treatment period. UFH given by continuous intravenous infusion was adjusted by aPTT; the mean dosage was 31,700 IU at day 1 and 35,800 IU at day 10. The duration of treatment was comparable for LMWH (12.5 ± 3.4 days) and UFH (11.4 ± 3.1 days).

**Venographic Findings**

Venographies at baseline and at the end of the initial treatment period were available in 596 of 797 patients (LMWH group n = 299 [76.1%] and UFH group n = __ Ie 297 [73.5%]). The absolute values of the Marder score __ Il
were 23.2 ± 8.4 and 23.9 ± 8.9 at entry for LMWH and UFH, respectively (2p = 0.23). At the end of the initial treatment, the values were 18.9 ± 9.7 and 20.5 ± 9.9 for LMWH and UFH, respectively (2p = 0.04), in favor of the LMWH treated group.

**Composite Outcome**

A total of 393 patients allocated to LMWH and 404 patients allocated to UFH were evaluated with regard to the composite outcome. At least one outcome measure of recurrent VTE, death, or major bleeding was observed during the initial treatment period in 5 patients (1.3%) receiving LMWH and in 20 patients (5.0%) receiving UFH (2p = 0.004) (Table 2). The analysis produced a statistically significant pooled RR of 0.26 (95% CI, 0.11 to 0.63) in favor of LMWH or a 74% reduction in risk of combined outcome for LMWH versus UFH. Major bleeding complications were the only item that occurred significantly less frequently in patients randomized to LMWH compared with those randomized to UFH. The data are given in Table 2. The cumulative incidence of the composite outcome is shown in Figure 1. In addition, the day of occurrence of the respective elements in the two treatment groups is given in Table 3.

**Marder Score and Recurrent Venous Thromboembolism**

The Marder score improved in 361 of 596 patients and did not improve in 235 patients with paired phlebographies. Four of the 235 patients with no improvement of the Marder score suffered from recurrent VTE: 1 patient of the LMWH group (0.3%) and 3 patients of the UFH group (1.0%). One patient randomized to UFH had an improved Marder score in the second venogram and experienced a pulmonary embolism. Two other patients with no second phlebography had recurrent VTE during treatment with UFH. Comparing patients without improvement of the Marder showed a trend for a higher frequency of recurrent VTE (2p = 0.08).

**DISCUSSION**

So far, clinical studies have shown that body weight–adjusted LMWHs, given subcutaneously, are at least as effective and safe as intravenous aPTT-controlled UFH for the initial treatment of patients with acute DVT. However, from a pharmacokinetic and clinical point of view it is unclear whether body weight adjustment of LMWHs is really necessary for the treatment of acute DVT. Recently, two consecutive, randomized clinical trials with the same study design proved the safety of a fixed, body weight–independent dose of the LWMH certoparin in patients with acute proximal DVT. In the initial studies, a relevant reduction of the Marder score of 30% on the second venography, as compared with the one obtained at entry, was defined. The choice of this relevant reduction was also based on the outcome of earlier

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**Table 1 Baseline Characteristics of Study Patients**

<table>
<thead>
<tr>
<th></th>
<th>LMWH n = 393</th>
<th>UFH n = 404</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60.6 ± 14.0</td>
<td>62.3 ± 13.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.1 ± 15.4</td>
<td>80.3 ± 15.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Male</td>
<td>216 (55.0)</td>
<td>227 (56.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>96 (24.6)</td>
<td>102 (25.4)</td>
<td>0.81</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>134 (34.2)</td>
<td>121 (30.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Surgery past 4 w</td>
<td>27 (6.9)</td>
<td>22 (5.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Bedrest past 4 w</td>
<td>59 (15.0)</td>
<td>73 (18.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Known cancer</td>
<td>41 (10.5)</td>
<td>41 (10.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td>32 (8.2)</td>
<td>44 (11.0)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*(Mean values ± standard deviation or number and percentage of patients)*

**Table 2 Composite Outcome of the Initial Treatment of Proximal Venous Thrombosis Using Fixed-Dose, Body Weight–Independent Subcutaneous LMWH, Certoparin, and Intravenous Adjusted-Dose UFH**

<table>
<thead>
<tr>
<th></th>
<th>LMWH n = 393</th>
<th>UFH n = 404</th>
<th>RR CI</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>1 (0.3)</td>
<td>6 (1.5)</td>
<td>0.17</td>
<td>0.03–1.10</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>4 (1.0)</td>
<td>14 (3.5)</td>
<td>0.29</td>
<td>0.11–0.83</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>5 (1.3)</td>
<td>20 (5.0)</td>
<td>0.26</td>
<td>0.11–0.63</td>
</tr>
</tbody>
</table>

na, not analyzed

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**Figure 1** Kaplan-Meier curves showing the incidence of the composite outcome events during the initial treatment (2p = 0.004 by the log-rank test).
studies\textsuperscript{12,18,19} that used a 20 or 30\% reduction in thrombus size as primary outcome. Not enough patients had a substantial, that is, 30\% or more, deterioration of the Marder score in the second phlebography to analyze a possible relation between the phlebographic changes and recurrent VTE. Therefore, in the present analysis, the results of the Marder score values of these two trials were pooled and showed a significant difference in the score after the initial treatment period in favor of LMWH.

So far, most clinical studies comparing LMWH with UFH in the treatment of acute DVT documented the incidence of death, recurrent VTE, and major bleeding complications separately. However, these outcomes are all relevant clinical events to patients and should therefore be combined. In patients with pulmonary embolism, the composite outcome events were significantly less frequent after the initial treatment with body weight--adjusted LMWH.\textsuperscript{23} In a recent study,\textsuperscript{19} the composite outcome was observed less frequently in patients with acute proximal DVT treated with fixed-dose, body weight--independent LMWH. The present data show that these results are confirmed after combining the data of the two studies. A recent meta-analysis addressed the question of whether differences in effectiveness and safety among different LMWH preparations can be observed. They concluded that despite some nonsignificant differences in the clinical results, the use of any of the LMWH preparations is reasonable, provided they are used in dosages that have been adopted in the clinical trials.\textsuperscript{13} The pooled analysis of the two studies presented here used the same LMWH, thus avoiding a bias caused by possible differences in the LMWH compounds.

Regression of thrombosis may still be regarded as a surrogate parameter that is independent from the clinical outcome. Therefore, we also focused on the analysis of the relation between the Marder score and recurrent VTE and mortality. The pooled analysis of the two studies produced no significant relation between a lack of thrombus regression and the occurrence of thromboembolic complications during initial treatment of acute proximal DVT. However, a trend in the relation between thrombus progression and clinically symptomatic recurrent VTE may be detected from the data. Therefore, the results remain to be confirmed before drawing a definite conclusion.

Major drawbacks of meta-analysis reviews are the failure to consider relevant variables, heterogeneous studies, and bias in the interpretation of data.\textsuperscript{14,15} Therefore, findings of analyses based on individual randomized trials with similar designs are needed and presented here. In the two trials,\textsuperscript{18,19} venographies were performed according to the same guidelines, were quantified according to the same scoring system, and were evaluated by central reading of two independent radiologists. These procedures as well as the independent conduct of the studies and the prospective nature of the trial designs minimized the potential bias. In contrast, noninvasive methods have been evaluated only for detection of first and recurrent DVT, and recommendations were made for symptomatic, asymptomatic, and pregnant patients.\textsuperscript{24} No such studies are available for documentation of the efficacy of a new anticoagulant treatment. Therefore, all patients still have to undergo a venography, which has to be evaluated independently for validation of new treatment regimen with regard to efficacy.\textsuperscript{8–10,13}

In summary, the analysis of the two studies showed that the thrombus size regressed more and that the composite outcome of recurrent VTE, mortality, and major bleeding was observed less frequently after initial treatment of acute proximal DVT with fixed-dose, body weight--independent LMWH compared with UFH. Of these items, major bleeding complications occurred less frequently in patients receiving LMWH. Further studies are undertaken to investigate whether these results hold during the period of oral anticoagulation.

ACKNOWLEDGMENTS

We gratefully acknowledge the contributions of the committees and investigators who participated in the studies. They are listed in the original publications.

REFERENCES

7. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the aPTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. Arch Intern Med 1997;157:2562–2568

AQ1: Au: Last sentence of Abstract reads ok?
AQ2: Au: Please cite ref. 9 before 10 or delete & renumber.
AQ3: Au: Rank or signed rank test?