Fixed-dose versus adjusted-dose low molecular weight heparin for the initial treatment of patients with deep venous thrombosis

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Patients with acute deep vein thrombosis (DVT) were treated with a body-weight independent dosage of 2 × 8000 aXa IU low-molecular-weight heparin (LMWH) Certoparin. After the subcutaneous administration of 8000 IU Certoparin, pharmacodynamic parameters did not differ between patients and healthy volunteers, and the AUC of the anticoagulant effects were not related to body weight. Two clinical trials demonstrated a greater regression of thrombi and a lower occurrence of recurrent venous thromboembolism (VTE), major bleeding, and mortality within 14 days of initial therapy compared with intravenous heparin. D-dimer decreased, and anti-Xa activity increased in those patients with a regression of thrombosis. The benefit of the reduced occurrence of recurrent VTE, major bleeding, and mortality was maintained up to 6 months. Major bleeding was not related to the body weight in either treatment group. Treatment of acute DVT in adults with fixed dose of 2 × 8000 aXa IU LMWH Certoparin is more effective and safer than heparin.

Manystudieshaveprovenanalmostequalefficacyandsafetyofsubcutaneouslow-molecular-weightheparins(LMWH)asintravenousunfractionatedheparin(UFH)fortheinitialtreatmentofpatientswithacutedeep-vein thrombosis (DVT) [1–3••]. It is suggested, that this is based on improved pharmacologic properties, including higher anti-Xa-activity compared with anti-IIa-activity, less binding to plasma proteins [4], prolongation of half-life, and high relative bioavailability of the subcutaneous administration [5,6], resulting in a more predictable anticoagulant response [7].

Low molecular weight heparins are usually administered in body-weight-adjusted doses twice per day subcutaneously [8••]. However, it is unclear from a pharmacokinetic and clinical point of view, whether body-weight adjustments of LMWH are really necessary for the treatment of patients with acute DVT. The anticoagulant effect of LMWH is more predictable than that of UFH, and consequently, monitoring is not mandatory for prophylaxis or treatment of patients with venous thromboembolism (VTE) [9]. Nevertheless, pharmacodynamic or pharmacokinetic studies of therapeutic doses of LMWHs in humans are required, because laboratory monitoring should be available for some patients. This is of special importance for the treatment of patients with DVT with a fixed, body-weight-independent dose of the LMWH Certoparin.

A higher reduction of the thrombus size was observed in patients with DVT treated with LMWH compared with UFH [10•]. An objective of the present analysis is to question the efficacy and safety of one LMWH based on the results of the Marder score from repeated ascending venography at entry [11•]. We have focused on the question, “whether D-dimer may be relevant in relation to the regression of thrombus size after treatment of DVT with aPTT-adjusted intravenous UFH or fixed-dose, body-weight-independent LMWH Certoparin.” We were interested specifically to whether differences of D-dimer and of other coagulation markers can be found after patients were treated with LMWH compared with UFH [12•].

Meta-analyses demonstrated a reduced occurrence of recurrent VTE and of mortality 3–6 months after patients were initially treated with LMWHs compared with UFH.
However, pooling of data from clinical studies may encounter difficulties such as homogeneity of patients and comparability of LMWHs [15]. A beneficial long-term clinical outcome has not yet been demonstrated for one LMWH alone based on three independent clinical trials after initial therapy of DVT. The availability of such studies would avoid the bias caused by differences of study designs, study population, treatment regimens, and origins of the LMWH preparations, pooling the data of clinical trials [16••,17••]. The studies aimed to demonstrate an improved outcome over at least 6 months for patients with acute DVT initially treated with LMWH.

**Materials and methods**

**Pharmacodynamics of fixed dose low-molecular-weight heparin in healthy volunteers and patients**

Eighteen male healthy volunteers aged 22–36 years participated in the single-dose, randomized, two-period crossover studies to receive 8000 IU of the LMWH Certoparin (Novartis Pharma GmbH, Nuremberg, Germany) subcutaneously [18•].

Four female and nine male patients with acute proximal DVT were enrolled in the study. They received 8000 aXa IU Certoparin (Monoembolex; Novartis Pharma GmbH, Germany) bid for the management of acute DVT for 12 days followed by oral anticoagulation over 6 months [19•].

Anti-Xa activities of Certoparin were measured with the chromogenic substrate S2222 and purified bovine factor Xa (normal range < 0.01 IU/mL) [20].

**Regression of thrombi during initial therapy**

The two studies [16••,21•] included 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 to Rabinov and Paulin [22•].

Patients were randomly assigned to therapy with 8000 international anti-factor Xa units (aXa IU) Certoparin bid subcutaneously or UFH with an initial bolus of 5000 IU followed by a continuous intravenous infusion at an initial rate of 20 IU/kg/h. The dose of UFH was subsequently adjusted to a target-activated partial thromboplastin time (aPTT) of two- to threefold the reference value. 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.

Patients underwent a second ascending venography of the affected leg between days 7 and 15, unless clinical symptoms prompted an earlier test. Two independent radiologists quantitatively assessed the thrombosed veins according to the scoring system of Marder et al. [11•]. 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 [16••].

**Regression of thrombi and coagulation markers**

The results of the coagulation markers were divided into the following groups: patients with improvement or no improvement of the Marder score in the second phlebography as compared with that at entry and treated with LMWH or UFH [12•].

Plasma samples were collected at days 1 and 12 (or at the end of heparin treatment, whatever came first) at 8 a.m. D-dimer assay (normal range: < 500 µg/L) was performed with commercially available reagents (Gold EIA; Agen Biomedical Limited, Acacia Ridge, Australia). Factor Xa inhibition was measured using the chromogenic substrate S 2222 (normal range < 0.01 heparin units/mL [20]). Hestest clotting assay was performed as described earlier [20]. Normal values ranged from 13 to 20 seconds. Thrombin inhibition was analyzed by the chromogenic S2238 substrate assay. Normal values were below 0.03 IU heparin/mL plasma [20].

**Outcome measures after 6 months**

The results of the two independent large studies [16••,17••] were combined for this analysis. An independent endpoint committee blinded for treatment groups evaluated all events evaluated recurrent thromboembolism, major hemorrhage, and mortality. The secondary outcome measure of the study was the composite outcome of recurrent VTE, major bleeding, and death during the 6-month follow-up period.

**Results**

**Pharmacodynamic parameters in healthy volunteers and patients with deep-vein thrombosis**

The pharmacodynamic parameters are given in Table 1 after the s.c. administration of 8000 IU Certoparin in healthy persons and in patients with acute DVT. Minor, if any, differences can be seen between the groups (Table 1). The body weight did not correlate with the area under the activity time curve of the anti-Xa activity (Fig. 1) [18•,19•].

**Regression of thrombi during initial therapy**

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. The dosage of LMWH was 8000 aXa IU bid subcutaneously throughout the treatment period and of UFH 31,700 IU.
at day 1 and 35,800 IU at day 10 by continuous intravenous infusion. The duration of treatment was comparable for LMWH (12.5 ± 3.4 days) and UFH (11.4 ± 3.1 days).

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 = 297 [73.5%] patients). The absolute values of the Marder Score were 23.2 ± 8.4 and 23.9 ± 8.9 at entry for LMWH and UFH, respectively ( \( P_s = 0.23 \)). At the end of the initial treatment, the values were 18.9 ± 9.7 and 20.5 ± 9.9 for LMWH and UFH, respectively ( \( P_s = 0.04 \) in favor of the LMWH treated group [23••]).

Regression of thrombi and coagulation markers

Coagulation markers have been investigated in a subgroup of patients [16••]. Plasma samples were taken at entry and after the 12 days heparin treatment period. Forty-eight and 41 patients were randomized to LMWH and UFH. Of these patients, 42 and 29 had an improvement, and 6 and 12 had no improvement of the Marder score at the end of therapy with LMWH and UFH, respectively. The dose of UFH was 30,885 ± 8074 IU/day at day 1 and was adjusted by determinations of the activated partial thromboplastin time during the treatment period (two- to three-fold prolongation of the aPTT), leading to 33,974 ± 10,572 IU/day at day 12.

Patients with an improved Marder score at day 12 showed lower D-dimer levels in both treatment groups ( \( P < 0.001 \)) and higher values of factor-Xa inhibition ( \( P < 0.002 \)) and of Heptest ( \( P < 0.03 \)) and lower thrombin inhibition ( \( P < 0.002 \)) in the LMWH group. It can be seen from the results that these coagulation markers showed lower values in those patients in whom the Marder score did not improve at the second phlebography. There was no correlation between the changes of the Marder scores and the changes of the coagulation markers [12••].

Clinical outcome after patients were initially treated with fixed-dose low molecular weight heparin

Three hundred and ninety-three patients allocated to LMWH and 404 patients allocated to UFH were evaluated. Recurrent VTE, death, or major bleeding was observed during the initial treatment period in five (1.3%) patients receiving LMWH and in 20 (5.0%) patients receiving UFH ( \( P_s = 0.004 \)). The analysis produced a statistically significant pooled RR of 0.26 (95% confidence interval [CI], 0.11–0.63) in favor of LMWH or a 74% reduction in risk of combined outcome for LMWH versus UFH. Major bleeding complication was the only item that was significantly less frequently occurring in patients randomized to LMWH compared with those randomized to UFH [23••].

Combined analysis of two studies on the clinical outcome at 6 months

The results of the [16••] two trials [17••] could be combined due to the almost identical trial design to analyze the combined outcome of recurrent venous thromboembolism, major bleeding, and mortality at 6 months [24••]. Of 1758 patients, 893 were assigned to receive LMWH and 865 to UFH. No differences in the baseline characteristics of the two treatment groups were detected. The mean (± SD) duration of anticoagulant treatment was 11.8 ± 2.8 days with LMWH and 10.7 ± 2.7 days with UFH, respectively (not significant). The doses of UFH were 1352 ± 340 IU per hour at day 1 and 1427 ± 476 IU per hour at day 10. Oral anticoagulation was started at day 8.2 ± 2.4 in patients on LMWH and at day 7.9 ± 2.1 in patients on UFH (not significant).

Venous thromboembolism re-occurred in 3.1% and 5.1% of patients initially allocated to LMWH and UFH, re-

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Table 1. Pharmacodynamic parameters after the subcutaneous administration of 8000 IU Certoparin in healthy individuals and in patients with acute deep vein thrombosis
Results show the combined analysis [15] of recurrent venous thromboembolism, major bleeding complications, and mortality for low-molecular-weight heparins (LMWH) and unfractionated heparin (UFH).

Figure 2 shows the results from patients treated with body-weight-adjusted s.c. LMWH [25•]. Figure 3 shows the RRR of the treatment of patients with DVT using body-weight-independent, fixed-dose Certoparin. All data give the incidences including the follow-up periods of 3–6 months (Fig. 2) and 6 months (Fig. 3). Data in Figure 2 were obtained with different LMWHs and different study design. Data for Figure 3 were from studies with the same LMWH, same dosage of the heparins, and the same study designs.

The relative risk of developing recurrent venous thromboembolism (VTE), major bleeding, or mortality during the initial treatment with Certoparin followed by 6 months oral anticoagulation is depicted [24••]. These data were obtained with low-molecular-weight heparin (LMWH) alone, in contrast to the data in Figure 2. All incidences are in favor of LMWH used for the initial treatment of patients with acute deep-vein thrombosis.
Regression of thrombosis may still be regarded as a surrogate parameter, which is independent from the clinical outcome. The pooled analysis of the two studies presented here used the same LMWH, thus, avoiding a bias caused by possible differences of the LMWH compounds. In the present analysis, the results of the Marder score values of these two trials were pooled and showed a significant difference of the score after the initial treatment period in favor of LMWH. The analysis of the two studies shows that the thrombus size decreased, and the composite outcome of recurrent VTE, mortality, and major bleeding was observed less frequently after the initial treatment of patients with acute proximal DVT with fixed-dose, body-weight-independent LMWH compared with UFH.

Measurement of D-dimer, a specific fibrin degradation product, demonstrated a decrease during heparin therapy. Lower D-dimer levels at day 5 were associated with an improved venographic outcome after 6 months [27]. D-dimer levels decreased in 10% of patients within 1–3 days, followed by a continuous slow decline towards the normal range [28]. A relation was demonstrated in the present study of a reduction of the size thrombi and D-dimer levels. The decrease of D-dimer occurred only in those patients who had a reduced Marder score at the end of therapy indicating the profibrinolytic potency of UFH and LMWH. Decreased D-dimer levels and increased aXa activities were related to a reduction of the Marder score during treatment with fixed, body-weight-independent dosage of LMWH for the treatment of patients with VTE. Based on these data it may be reconsidered that coagulation parameters should be monitored to improve the treatment strategy with LMWH.

The data of the pooled analysis of these two independent studies demonstrates that the initial treatment of patients with acute VTE with the LMWH Certoparin reduces the re-occurrence of VTE during the initial treatment period compared with UFH. This effect is maintained at least for the 6-month follow-up during oral anticoagulant therapy. The present analysis demonstrates the reduced incidences of clinical endpoints during therapy with one LMWH preparation alone compared with other analyses pooling data of trials with different LMWHs.

The present overview demonstrates the improved efficacy and safety of a single LMWH for the treatment of patients with acute DVT compared with UFH using a fixed, body-weight-independent dosage of Certoparin. This regimen offers an alternative to body-weight-adjusted dosage of LMWHs for the initial treatment of patients with acute DVT.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
•• Of outstanding interest

This is the first study, demonstrating with sufficient power the equal efficacy and safety of subcutaneous body-weight-adjusted low-molecular-weight heparin compared with intravenous unfractionated, dPTT-controlled heparin for the initial treatment of patients with deep vein thrombosis. Main endpoint was 3 months after study incidence of recurrent venous thromboembolism.


In the same issue of the New England Journal of Medicine is reference 1 (Levine et al., N Engl J Med 1996, 334:677–681). A second study with a different LMWH-heparin appeared, demonstrating the equal efficacy and safety of body-weight-adjusted subcutaneous LMWH as compared with intravenous unfractionated heparin for the treatment of patients with acute deep venous thrombosis. The main endpoint was the recurrent rate of thromboembolism 6 months after the initial event.


The study was important to demonstrate the improved reduction of thrombus size during LMWH compared to UFH in patients with deep vein thrombosis. Recurrent thromboembolism after 3 months was related to the reduction of thrombus size after the initial heparin treatment.
Clinical study showing the proven efficacy and safety profile of fixed-dose body-weight-dependent subcutaneous LMWH for the initial treatment of proximal deep venous thrombosis (DVT). Thromb Haemost 2001, suppl:OC 1645.

Clinical study comparing the fixed-body-weight-independent subcutaneous dosage of LMWH to intravenous unfractionated heparin on the incidence of recurrent thromboembolism 6 months after the initial treatment.

Clinical study in DVT patients demonstrating the lack of dependence of fixed-dose LMWH from the body weight for determination of the area under the activity time curve of the anti-factor Xa activity.

Clinical study comparing intraovenous and subcutaneous LMWH for treatment of patients with acute DVT.


Comparison of an improved efficacy and safety of low-molecular-weight heparins in the treatment of patients with acute deep-vein thrombosis demonstrating the long-term benefit of an initial therapy of DVT with LMWH.

Clinical study in patients with acute deep venous thrombosis treated with fixed-dose subcutaneous LMWH for the initial treatment of patients with DVT compared with intravenous UFH.


Comparison of an improved efficacy and safety of low-molecular-weight heparins in the treatment of patients with acute DVT. The conclusion is the comparability of the different LMWHs. However, differences between the LMWHs can also be observed.

Clinical study showing the proven efficacy and safety profile of fixed-dose body-weight-independent subcutaneous LMWH for the treatment of patients with acute DVT compared with intravenous unfractionated heparin. First study design using a combined clinical endpoint consisting of the current thromboembolism, major-bleeding complications, and mortality 6 months after the initial event.

Analysis of two studies demonstrating a significant higher reduction of thrombus size using fixed-dose subcutaneous LMWH for the initial treatment of patients with DVT compared with intravenous UFH.

Comparison of an improved efficacy and safety of low-molecular-weight heparins in the treatment of patients with acute DVT. The conclusion is the comparability of the different LMWHs. However, differences between the LMWHs can also be observed.