Fixed-dose, body weight-independent subcutaneous low molecular weight heparin Certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis

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Summary

Subcutaneous body weight-adjusted low molecular weight heparin (LMWH) has been proven as effective and safe as intravenous aPTT-adjusted unfractionated heparin (UFH) for the treatment of patients with acute deep venous thrombosis (DVT). In this study we evaluate the efficacy of the initial treatment of proximal DVT with a fixed-dose, body weight-independent application of the LMWH Certoparin with a six month follow-up.

In a prospective, multicentre, randomized, active-controlled study 1220 patients with objectively diagnosed proximal DVT were randomly assigned to subcutaneous 8000 U anti-factor Xa of Certoparin twice daily for 10 to 14 days or intravenous aPTT-adjusted UFH for 5 to 8 days. Both regimen were followed by oral anticoagulation for 6 months. The primary end point was the rate of symptomatic and objectively confirmed thromboembolic events within 6 months. The aim of the study was to demonstrate the non-inferiority of the Certoparin regimen as compared to UFH.

The per-protocol analysis revealed 22 (3.8%) thromboembolic events in the Certoparin group and 24 (4.3%) in patients assigned to UFH within 6 months, thereby proving the non-inferiority (p<0.01), confirmed by intent-to-treat analysis (p<0.001). Major bleeding occurred in 6 and 7 patients started on Certoparin or UFH during the treatment period. Thromboembolic events were equally distributed in body weight categories with <50, 50-80 and >80 kg as followed: 0, 3.6% and 4.1% of patients for the Certoparin group and 0, 4.6% and 4.2% of patients for the UFH group. The same was true for major bleeding complications with 0, 2.9% and 1.5% for Certoparin and 0, 3.5% and 4.2% for UFH. Overall mortality was 1.9% in the Certoparin group and 2.7% in the UFH group.

Fixed-dose body weight-independent subcutaneous LMWH Certoparin is at least as efficacious and safe as intravenous aPTT-adjusted UFH for the initial treatment of acute proximal DVT. This effect is maintained during a 6-months follow-up of treatment with oral anticoagulation.
Introduction

Although anticoagulation therapy with heparin and vitamin K antagonists is the treatment of choice for most patients with acute venous thromboembolism, the optimal use of this treatment strategy remains to be defined. In recent years low molecular weight heparins (LMWHs) have become available as alternatives to unfractionated heparin (UFH) (1-3). LMWHs have some potential advantages as compared to UFH such as a longer plasma half-life, a lower variability of the anticoagulant response and an almost complete bioavailability after subcutaneous administration. Most of the studies with LMWH in patients with acute deep venous thrombosis (DVT) or pulmonary embolism have been performed using body weight adjusted dosages (4). However, as the distribution volume of heparins do not vary to a greater extent in relation to body weight, it is unclear from a pharmacokinetic point of view, whether body weight adjustment of LMWHs is really necessary for the treatment of acute DVT. Moreover, application of a fixed dose of the LMWH Certoparin in patients with venous thromboembolism in two previous clinical trials demonstrated a greater reduction of thrombus size during initial therapy as compared to UFH (5-7). It was the purpose of the present study TH-4 to demonstrate definitively that the initial treatment of acute proximal DVT with fixed-dose, body-weight-independent subcutaneous Certoparin was not inferior to UFH with regard to efficacy, i.e. the recurrence of symptomatic venous thromboembolism, and safety, e.g. bleeding and mortality, over 6 months.

Methods

Study design

In a prospective, multicenter, randomized, active-controlled, open-label trial the initial therapy with intravenous application of UFH was compared to the subcutaneous application of a fixed-dose body weight-independent administration of the LMWH Certoparin twice a day in patients with DVT. All patients received overlapping oral anticoagulation (vitamin K antagonists) up to the end of a 6-month follow-up. A total of 121 centres in Germany and the Czech Republic participated in the trial. The local or national institutional review boards approved the protocol and the study was conducted in accordance with national and international regulations.

Patients

Patients of at least 18 years of age were included in this trial with clinical symptoms of acute proximal DVT for fewer than 3 weeks, verified by venography or ultrasonography, after having given written informed consent. Exclusion criteria were: isolated calf-vein thrombosis, planned fibrinolysis or operation, clinically severe pulmonary embolism (stage II and III), heparin application within 8 days before enrollment (except treatment in the past 24 h), treatment with oral anticoagulants for more than 24 hours before the start of study medication, hypertension with systolic values >200 mm Hg and diastolic values >105 mm Hg despite antihypertensive treatment, known malignant tumour as local cause of venous occlusion, severe renal or hepatic insufficiency, surgery of the head, chest and abdomen in the past eight days, intervention in the central nervous system in the past 14 days, evident disseminated intravascular coagulation, clinical condition with an increased risk of bleeding complications during the planned treatment time, gastrointestinal bleeding or gastric ulcer in the past 4 weeks, contraindications against oral anticoagulants or known intolerability against heparin, platelet count < 100000/µl, pregnancy, treatment with platelet inhibitors (with exception of acetylsalicylic acid in a dosage up to 100 mg/day). Randomisation of patients was carried out using a central telephone system. The assignment to one of the treatment groups was documented and could not be changed afterwards.

Treatments

Immediate anticoagulation was started in hospital. Patients of the UFH group received an initial intravenous bolus of 5000 IU, followed by continuous infusion of aPTT (activated partial thromboplastin time) -adjusted UFH with a starting dose of 20 IU/kg/h for 5 to 8 days. Dosage of UFH was modified in order to achieve a prolongation of the aPTT of 1.5-2.5 times of the centre-specific upper limit of the normal range. From day 1 or 2 all patients received additionally vitamin K antagonists. Patients randomized to LMWH (Certoparin, Mono-Embolex®, Novartis Pharma GmbH, Nuremberg, Germany) received twice daily 8000 U anti-factorXa subcutaneously for 10 to 14 days. Between days 7 to 10 oral anticoagulation was started. Application of heparin was terminated when the international normalized ratio (INR) was > 2.0 for at least two consecutive days and this ratio was subsequently maintained. Anticoagulation started within the hospital and – according to the patient’s condition and the local possibilities – treatment was continued out of hospital.

Primary and secondary endpoints

Primary endpoint was the incidence of thromboembolic complications at day 190 (according to the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease by the Committee for Proprietary Medicinal Products, CPMP). Thromboembolic complications were defined as (i) recurrence of symptomatic, objectively documented DVT, (ii) occurrence of symptomatic, objectively documented pulmonary embolism and (iii) death, in which another reason other than thromboembolism was not clearly documented as cause of death. Secondary endpoints were the individual incidences of DVT, pulmonary embolism, and fatal pulmonary embolism. All events were evaluated by
an independent endpoint committee blinded for treatment groups.

In addition, the incidence of venous thromboembolism was analysed separately for the initial treatment and the follow-up period. Initial treatment was defined as the period between the first and the last administration of heparin treatment. The follow-up was defined as the period between the last administration of the study medication and day 190. For additional subanalysis patients were subdivided in three prospectively defined body weight classes of <50 kg, between 50 and 80 kg and >80 kg to analyse a relation of body weight to the fixed dosage of Certoparin as compared to aPTT-adjusted UFH.

Adverse events
Serious adverse events and especially all bleeding complications were evaluated by an independent Safety Committee whose members were blinded for the treatment group. Major bleedings were defined as follows: a fall of hemoglobin >2.0g/dl or transfusion requirement of more than two units of packed red cells or retroperitoneal or intracranial or intraspinal hemorrhage or premature discontinuation of treatment due to any other bleeding. Thrombocytopenia was defined as a drop of platelet count to <80,000/µl or ≤50% of the baseline value.

Statistical analysis
The aim of the trial was to prove non-inferiority of Certoparin versus UFH regarding the incidence or recurrent venous thromboembolism at 6 months. The lower limit of equivalence for confirmatory analysis had prospectively been fixed at 3%. The study was performed according to the adaptive design proposed by Bauer and Köhne (8). Thereby the sample size of the second part of the study was mainly based on the results of part 1. Decision making after part 1 of the study was done by an independent Data Monitoring Committee. In part 1 of the study 499 patients were included, part 2 comprised 635 per-protocol patients. The per-protocol sample was used for confirmatory testing of the null hypothesis. Protocol violations leading to exclusion from the per-protocol sample were defined in the Blind Review Meeting. Intent-to-treat analysis was used to explore the sensitivity of the per-protocol results; the intent-to-treat sample was identical with the safety sample. The global one-sided level of significance was set to 0.025, and the method of Blackwelder was applied to calculate one-sided p-values for both parts of the study at a non-inferiority limit of 3% using Fisher’s combination test (9). One-sided confidence intervals (which were constructed using the method of repeated confidence intervals according to Jennison and Turnbull (10), treatment differences and relative risk reductions were calculated. Frequencies of secondary endpoint events and safety data were compared by Fisher’s exact test (two-tailed) disregarding the two-stage design.

Results

Study patients
A total of 1229 patients with objectively verified, symptomatic proximal DVT were enrolled. Nine patients, 6 and 3 in the UFH and Certoparin group, respectively, did not receive study medication. Of the remaining 1220 patients, 627 were allocated to Certoparin and 593 patients received UFH (safety sample = intent-to-treat sample). Most frequent protocol violations leading to exclusion from the per-protocol population were forbidden concomitant medication (53 patients), violation of the randomization (39 patients) and lost to follow-up (22 patients); therefore, the per-protocol population consisted of 578 patients treated with Certoparin and 556 patients treated with UFH. The patients characteristics of the two treatment groups were comparable at baseline (Table 1). A pulmonary embolism at the time of inclusion had been verified in 6.7% of UFH patients and 9.1% of Certoparin patients.

Study medication
The adjustments of the aPTT above the minimal effective limit of 1.5 [2] times of the centre specific upper limit of the normal range were at day 1: 42.3 [29.7] %, at day 2: 81.2 [66.8] %, at day 3: 89.3 [75.9] %, and after days 4 to 8 of UFH treatment: more than 90 [80] % (93.0 to 97.6 [83.2 to 94.7] %) of the patients. The mean duration of heparin treatment was 7.7 ± 2.4 days with UFH and 12.1 ± 2.4 days with Certoparin. With respect to the oral anticoagulation an INR >2 was obtained in 77.7% of the patients within the UFH group and in 73.9% within the Certoparin group at the end of heparin treatment. Respective values after one and six months were 81.7% (UFH) vs. 80.7% (Certoparin) and 86.9% vs. 88.6%.

Recurrent venous thromboembolism
With respect to the per-protocol sample 24 patients of the UFH group (4.3%) experienced at least one thromboembolic event during the complete study period of 6 months as compared to 22 patients of the Certoparin group (3.8%). The result of the combination test (0.0003) as the confirmatory statistical analysis of the adaptive group-sequential study showed the non-inferiority of Certoparin to UFH. The lower limit of the confidence interval was −1.89%. The point estimate of the treatment difference was 0.51% in favour of Certoparin, the relative risk reduction was 11.8% (Table 2). The intent-to-treat analysis confirmed the results of the primary per-protocol analysis. Overall 27 patients of the UFH group (4.5%) suffered from a thromboembolic complication as compared to 22 patients of the Certoparin group (3.5%). The respective result of Fisher’s combination test was 0.00002, the lower limit of the confidence interval was −1.21%, the treatment difference was 1.04% with a relative risk reduction of 22.9%. Additionally, Table 2 shows the distribution of thromboembolic events during the heparin treatment period and during 6 months follow up.
Safety

Bleeding complications occurred in 74 patients (11.8%) treated initially with Certoparin and in 64 patients (10.8%) with UFH (Table 3). During the initial treatment period bleeding complications occurred in 19 patients treated with Certoparin (3.0%) versus 24 patients treated with UFH (4.0%). Six bleeding episodes within the Certoparin group (1.0%) as well as 7 within the UFH group (1.2%) were considered as major. Follow-up with oral anticoagulation resulted in another 57 (9.4%) and 44 (7.6%) bleeding complications in the Certoparin and in the UFH group, respectively. Differences were not statistically significant.

Thrombocytopenia occurred in 11 Certoparin patients (1.8%) as well as in 11 UFH patients (1.9%). Overall, that means during the complete study, 12 patients of the Certoparin group (1.9%) and 16 patients receiving UFH died (2.7%) (Table 4). There was no fatal hemorrhage.

Relation to body weight

Body weight distribution showed a wide range from 42 to 163 kg. Thromboembolic complications and major bleedings occurred with comparable frequency in both groups with regard to body weight <50 kg, between 50-80 kg and >80 kg (Table 5). Results were shown for the per-protocol as well as the intent-to-treat sample.
Discussion

Prophylaxis of thromboembolism with LMWH by body weight independent fixed dosages is a widely accepted standard treatment, but therapy of acute DVT by a fixed dose in adults is reasonable, too, as the distribution volume (intravascular space) of LMWH demonstrates only a weak relationship to body weight. In two randomised prospective trials Kirchmaier et al. (5) and Harenberg et al. (6) demonstrated that a fixed-dose of 8.000 U aXa of Certoparin twice daily subcutaneously given for 10 to 14 days resulted in a superior regression of phlebography-controlled thrombus size (reduction of Marder score) compared to UFH. However, the clinical relevance of a reduction of the Marder score is still debated for patients with venous thromboembolism. Therefore, meta-analyses were performed pooling the results obtained with different LMWH preparations. The results differ in minor points, but they show, that body weight adjusted LMWHs are at least as effective and safe as aPTT-controlled UFH for the initial treatment of acute DVT. Furthermore, these meta-analyses demonstrate a trend in favour of LMWH with respect to the incidences of recurrent thromboembolism, major bleeding complications and mortality (13-16). The present study proved the non-inferiority of a body weight independent fixed dose of Certoparin as compared to aPTT-adjusted UFH with a slight tendency in favour of Certoparin. An important point in the discussion of UFH treatment result is whether a sufficient adjustment of UFH within the target range was achieved. At day 1, 2 and 4 more than 40, 80, 90% of the patients, respectively, were adequately adjusted in this study. However, this situation seems not only to represent a cross-section of the real life conditions reflected in the more than 120 participating study centres, but is well within the range of other clinical trials. For example, Breddin et al. recently reported that in 67% of the study patients treated with UFH, the target range (1.5 to 2.5 times the baseline level) was reached within 24 to 48 h (17). This discussion is further complicated by the varying sensitivities of different aPTT reagents to monitor heparin therapy and the failure to clearly demonstrate the prognostic value of subtherapeutic aPTT responses on subsequent recurrent venous thromboembolism (18). At the end of heparin treatment around 75% of patients showed an intensity of oral anticoagulation with INR >2. This percentage is not given in several recent study reports, but tends to be slightly lower as known from older clinical studies, however, both treatment groups were equally concerned.

LMWHs, especially Certoparin, have a more profound fibrinolytic potential as compared to UFH (19). Based on these observations in a previous pilot study, the duration of treatment with Certoparin was extended to two weeks (20). Thrombus regression was determined by phlebography at the end of week 1 as well as week 2, and it was confirmed that prolongation of the study definitively proved the non-inferiority of the initial treatment of acute proximal DVT with a body weight independent fixed dosage of the LMWH Certoparin.

LMWH compounds are fragments of UFH obtained by controlled enzymatic or chemical depolymerization processes. Consequently, the LMWH preparations differ in their anti-factor Xa and anti-thrombin ratios and pharmacokinetic properties (11). This may result in differences of the efficacy and safety profile of the LMWH preparations for treatment of venous thromboembolism. Van der Heijden, et al. suggested that Certoparin reveals a very favourable relationship between efficacy and safety using linear regression analysis (12). Because of the relatively small number of patients randomized in individual clinical trials, most studies failed to demonstrate statistically significant differences between LMWH preparations and UFH in the treatment of acute DVT. Therefore, meta-analyses were performed pooling the results obtained with different LMWH preparations. The results differ in minor points, but they show, that body weight adjusted LMWHs are at least as effective and safe as aPTT-controlled UFH for the initial treatment of acute DVT. Furthermore, these meta-analyses demonstrate a trend in favour of LMWH with respect to the incidences of recurrent thromboembolism, major bleeding complications and mortality (13-16). The present study proved the non-inferiority of a body weight independent fixed dose of Certoparin as compared to aPTT-adjusted UFH with a slight tendency in favour of Certoparin. An important point in the discussion of UFH treatment result is whether a sufficient adjustment of UFH within the target range was achieved. At day 1, 2 and 4 more than 40, 80, 90% of the patients, respectively, were adequately adjusted in this study. However, this situation seems not only to represent a cross-section of the real life conditions reflected in the more than 120 participating study centres, but is well within the range of other clinical trials. For example, Breddin et al. recently reported that in 67% of the study patients treated with UFH, the target range (1.5 to 2.5 times the baseline level) was reached within 24 to 48 h (17). This discussion is further complicated by the varying sensitivities of different aPTT reagents to monitor heparin therapy and the failure to clearly demonstrate the prognostic value of subtherapeutic aPTT responses on subsequent recurrent venous thromboembolism (18). At the end of heparin treatment around 75% of patients showed an intensity of oral anticoagulation with INR >2. This percentage is not given in several recent study reports, but tends to be slightly lower as known from older clinical studies, however, both treatment groups were equally concerned.

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| Table 5: Thromboembolic and major bleeding events in relation to body weight |
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| Thromboembolic events | Per-Protocol sample | Intent-to-Treat sample* |
| Treatment group | Body weight (kg) | Patients | Patients with VTE (%)*** | Patients | Patients with VTE (%)*** |
| UFH | < 50 | 8 | 0 | 8 | 0 |
| 50-80 | 285 | 13 (4.6%) | 310 | 16 (5.2%) |
| > 80 | 263 | 11 (4.2%) | 275 | 11 (4.0%) |
| Certoparin | < 50 | 4 | 0 | 4 | 0 |
| 50-80 | 306 | 11 (3.6%) | 334 | 11 (3.3%) |
| > 80 | 268 | 11 (4.1%) | 289 | 11 (3.8%) |
| Major bleeding events | Per-Protocol sample | Intent-to-Treat sample* |
| Treatment group | Body weight (kg) | Patients | Patients with major bleeding (%)*** | Patients | Patients with major bleeding (%)*** |
| UFH | < 50 | 8 | 0 | 8 | 0 |
| 50-80 | 285 | 2 (0.7%) | 310 | 2 (0.6%) |
| > 80 | 263 | 5 (1.9%) | 275 | 5 (1.8%) |
| Certoparin | < 50 | 4 | 0 | 4 | 0 |
| 50-80 | 306 | 6 (2.0%) | 334 | 6 (1.8%) |
| > 80 | 268 | 0 | 289 | 0 |

* identical with safety sample
** events during complete study
treatment period resulted in a stronger reduction of the Marder score. Therefore, in the following clinical trials, including the present study, Certoparin was given for a duration of two weeks. In the TH-4 study the mean duration of treatment was 7.7 days within the UFH group and 12.1 days within the Certoparin group. However, the planned (“unbalanced”) prolongation of the initial heparin treatment in the Certoparin group did not increase the number of recurrent venous thromboembolism nor the rate of bleeding complications. Very recently in a three armed study with more than 1100 patients with DVT it had been demonstrated that prolongation of the initial therapy with LMWH did not result in a higher proportion of patients with venographic thrombus regression nor in differences in clinical study endpoints (17). Therefore, it may be speculated that the prolonged treatment phase with Certoparin is not mandatory.

Despite the relative constant distribution volume of 8,000 U x aXa of Certoparin twice daily may result in a under- or over-dosage in adults with increased (>80 kg) or decreased (<50 kg) body weight. Results of the predefined subgroup analysis seem to raise no concerns regarding increased incidences of recurrent venous thromboembolism in the high body weight group or increased bleeding complications in the low body weight group. However, the number of patients with body weight <50 kg was rather low, so, it is difficult to draw clinical relevant conclusions.

Recently, several trials have demonstrated that it is possible to treat DVT using a once-daily application of LMWH as compared to the more conventional twice-daily application regimen. From the studies published so far it was derived that LMWH once daily was as effective and safe as LMWH twice daily or UFH (17, 21–23). But a meta-analysis (24) including a total of 1522 patients was unable to exclude the possibility of a higher frequency of fatal bleeding induced by the higher peak levels obtained with once-daily therapy with LMWH. Nevertheless, once-daily Certoparin would have been even more convenient for the patients, however, this application regimen was not tested in previous clinical studies, but should be the aim of future trials.

In conclusion, fixed, body weight independent application of the LMWH Certoparin was proved to be at least as effective and safe in the initial therapy of proximal DVT as aPTT-adjusted intravenous UFH and thus definitively confirmed the results of previous clinical trials (5-6). The twice-daily subcutaneous regimen without dose adjustment according to body weight offers a simplified treatment for patients with acute deep venous thrombosis.

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Abbreviations
aPTT: activated partial thromboplastin time
DVT: deep venous thrombosis
INR: international normalized ratio
LMWH: low molecular weight heparin
UFH: unfractionated heparin

Addendum
The following committees participated in the study:

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References


