

Comparison of six-month outcome of patients initially treated for acute deep vein thrombosis with a low molecular weight heparin Certoparin at a fixed, body-weight-independent dosage or unfractionated heparin

JOB HARENBERG, HANNO RIESS, HARRY R. BÜLLER, JOACHIM BROM, GOTTFRIED WEIDINGER, MENNO V. HUISMAN

Background and Objectives. Body weight-adjusted subcutaneous low molecular weight heparin (LMWH) has been proven to be more effective and safer than aPTT-adjusted intravenous unfractionated heparin (UFH) for the initial treatment of patients with acute symptomatic deep venous thrombosis (DVT) based on analyses pooling the results of studies with different LMWHs. We investigated whether these findings hold for a particular LMWH by pooling the results of two independent studies.

Design and Methods. Patients with acute symptomatic proximal DVT (n=1758), proven by ascending phlebography or compression ultrasound, received either a fixed, body weight independent dose of 8,000 IU Certoparin b.i.d. (n=893) for 8.6 days or intravenous UFH (n=865) adjusted to an 1.5 to 3.0-fold prolongation of the aPTT for 12.0 days both followed by vitamin K-antagonists for 6 months.

Results. Venous thromboembolism (VTE) re-occurred in 5.1% and 3.1% (RRR 0.62, CI 0.39-0.98, 2p=0.04), major bleeding in 3.5% and 1.9% (RRR 0.55, CI 0.31-0.99, 2p=0.05), mortality in 3.6% and 2.1% (RRR 0.59, CI 0.34-1.04, 2p=0.08), and the composite outcome of all three events in 10.3% and 6.3% (RRR 0.61, CI 0.44 to 0.84, 2p=0.002) of patients at 6 months initially randomised to UFH and LMWH, respectively.

Interpretation and Conclusions. The initial treatment of acute DVT with a fixed dose of the LMWH, certoparin, is more effective in reducing, over 6 months, the re-occurrence of VTE and the composite outcome of recurrent VTE, major bleeding, and mortality without any relation of the bodyweight of the patients to recurrent venous thromboembolism or major bleeding complications.

Key words: bleeding complication, deep vein thrombosis, low molecular weight heparin, thromboembolism.

Haematologica 2003; 88:1157-1162
http://www.haematologica.org/2003_10/1157.htm

©2003, Ferrata Storti Foundation

Individual studies have shown a comparable or better efficacy and safety of subcutaneous body-weight adjusted low molecular weight heparin (LMWH) as compared to intravenous unfractionated heparin for the initial treatment of patients with acute deep vein thrombosis.¹⁻³ It is generally accepted that LMWH therapy does not require anticoagulant monitoring.⁴ This is based on the pharmacological properties of these drugs, including less binding to plasma proteins such as fibrinogen, platelet factor 4, alpha-1 acid glycoprotein, and to platelets, macrophages and granulocytes.⁵ Less binding to platelets results in a reduced risk of bleeding complications and less binding to macrophages results in a higher bioavailability of nearly 100%. The biological half-life on factor Xa inhibition is twice as long as for unfractionated heparin,^{6,7} resulting in a more predictable anticoagulant response.⁸ However, the necessity of adjusting the dose of LMWH to the patient's body-weight has not been established and is questionable given the distribution volume of LMWH in humans.

Meta-analyses demonstrated a lower incidence of recurrent venous thromboembolism, major bleeding and mortality 3 to 6 months after initial treatment with LMWH than after treatment with unfractionated heparin.⁹⁻¹¹ However, pooling data from clinical studies may encounter difficulties such as the comparability of low molecular weight heparins.¹² One recent analysis demonstrated differences in venous thromboembolism recurrence and major hemorrhage rates dependent on the type of LMWH.¹³ On the other hand, another study showed that the efficacy of two LMWH preparations was similar if proven effective doses were used to treat acute deep vein thrombosis.¹⁴

To document the efficacy and safety of a single LMWH, two independent clinical studies were performed with an almost identical study design.^{15,16} We took advantage of this similarity and pooled the outcomes in order to assess the efficacy and safety outcomes over six months in patients with acute deep vein thrombosis treated initially with LMWH certoparin.

Design and Methods

Study design

The two studies^{15,16} were multicenter, randomized clinical trials comparing fixed-dose, body weight-independent subcutaneous LMWH with aPTT-controlled intravenous unfractionated heparin in patients with acute proximal deep vein thrombosis. In the participat-

From the IV Dept. of Medicine, University Hospital Mannheim, Ruprecht-Karls University Heidelberg, Mannheim, Germany (JH), Humboldt University, Berlin, Germany (HR), Academic Medical Centre, University of Amsterdam, The Netherlands (HRB), Novartis Pharma GmbH, Nuremberg, Germany (JB, GW), Dept. of General Internal Medicine, University of Leiden, The Netherlands (MVH).

Correspondence: Professor Job Harenberg, M.D., IV. Dept. of Medicine, University Hospital, Theodor-Kutzer-Ufer 1, D-68167 Mannheim, Germany
E-mail: j-harenberg@t-online.de

ing countries treatment is routinely given with dose-adjusted intravenous unfractionated heparin in hospitalized patients. Patients ≥ 30 years of age with acute symptomatic proximal deep vein thrombosis (i.e. thrombosis in the popliteal or more proximal vein) documented by ascending venography according to Rabinov and Paulin¹⁷ or by compression sonography,¹⁸ were eligible. Patients were excluded from the study if they had one of the following: indication for surgical or fibrinolytic treatment of deep vein thrombosis, duration of symptoms exceeding 3 weeks, ongoing oral anticoagulation with vitamin K antagonists, renal failure, severe hypertension, severe hepatic failure, currently active bleeding, pregnancy, any operation within the past 8 days, acute severe pulmonary embolism, platelet count $< 100,000/\mu\text{L}$, and treatment with heparin > 24 h before inclusion into the study. The studies were carried out according to the guidelines of the Declaration of Helsinki. The study protocol was approved by all institutional review boards. All patients had to give written informed consent prior to randomization.

Treatment regimes

Patients received either a fixed dose of 8,000 anti-factor Xa international units (aXa IU) of certoparin (Mono-Embolex® Therapie, Novartis Pharma, Nuremberg, Germany) *b.i.d* subcutaneously for 10 to 14 days or unfractionated heparin with an initial bolus of 5,000 IU followed by a continuous intravenous infusion at an initial rate of 20 IU/kg/h. The duration of the initial therapy with unfractionated heparin was 10 to 14 days in the first study¹⁵ and 5 to 8 days in the second study;¹⁶ this difference was the result of changes of the national recommendations. The dose of unfractionated heparin was subsequently adjusted to a target activated partial thromboplastin time (aPTT) of 1.5 to 3-fold the reference value. The aPTT-tests were performed 4–6 hours after the start of treatment and if dose adjustment was required, the aPTT was repeated after 6 hours.

Treatment with vitamin K antagonists was started within the first week and continued for 6 months. Treatment with the LMWH or unfractionated heparin was stopped as soon as the international normalized ratio (INR) was above 2.0 for 2 consecutive days.

Primary outcome measure

Objectively confirmed symptoms of recurrent venous thromboembolism over 6 months were a secondary outcome measure in the first study. The combination of objectively confirmed symptomatic recurrent venous thromboembolism during the 6 months of follow-up and mortality not caused by diseases other than pulmonary embolism was the primary outcome in the other study. Recurrent

thromboembolic complications were defined as deep vein thrombosis, pulmonary embolism or death due to pulmonary embolism. Patients with suspected recurrent deep vein thrombosis underwent ascending venography. Patients in whom pulmonary embolism was clinically suspected underwent ventilation-perfusion scanning. Pulmonary embolism was diagnosed if a high probability perfusion defect was documented¹⁹ or if pulmonary angiography showed emboli. In case of death, autopsy was performed whenever permission was obtained.

Other outcome measures

Other outcomes were major bleeding and death as well as the composite outcome of all three events during the initial therapy and the 6-month follow-up period. Bleeding was defined as major if it was overt and associated with a decrease of the hemoglobin concentration by at least 2g/dL or if a transfusion of more than 2 units of blood was indicated or if the bleeding was intracranial or retroperitoneal. An independent and blinded adjudication committee evaluated all outcomes.

Statistical methods

The analysis was performed on an intention-to-treat basis. The two treatment groups were compared using Fisher's exact test, the t-test for independent data or the χ^2 test. To compare for study effects the Cochran-Mantel-Haenszel test and the Breslow-Day test for homogeneity of odds ratios were used (on medication by event by study) for thromboembolic and major bleeding events. A logistic regression model was used to investigate the relationship between thromboembolic events or major bleedings and study medication and body weight. Relative risks and the corresponding 95% confidence intervals were calculated using Mantel-Haenszel estimates.

Results

One thousand seven hundred and fifty-eight patients randomly received either unfractionated heparin or LMWH after objective confirmation of the diagnosis of acute deep vein thrombosis. Of these, 893 were assigned to receive subcutaneous LMWH and 865 to intravenous unfractionated heparin. No differences in the baseline characteristics of the two treatment groups were detected (Table 1).

Anticoagulant therapy

The mean (\pm SD) duration of anticoagulant treatment was 8.6 ± 2.8 days with unfractionated heparin and 12.0 ± 2.6 days with LMWH, the difference being due to the shorter treatment period with unfractionated heparin in the second study.¹⁶ The doses of unfractionated heparin were

Table 1. Baseline characteristics of the two treatment groups.

| Characteristic | Low molecular weight heparin n=893 | Unfractionated heparin n=865 | p values (2 p) |
|---------------------------------|---------------------------------------|---------------------------------|-------------------|
| Characteristic | | | |
| Age (yr., mean + SD) | 60.7±14.4 | 61.5±14.6 | 0.23 |
| Weight (kg, mean + SD) | 81.3±15.7 | 80.6±15.1 | 0.37 |
| Gender-female (%) | 44.2 | 43.6 | 0.81 |
| Predisposing factors (%) | | | |
| Previous VTE* | 14.3 | 16.7 | 0.16 |
| Varicose veins | 13.3 | 11.3 | 0.19 |
| Surgery in past 4 weeks | 3.0 | 2.5 | 0.57 |
| Previous bedrest > 3 days | 10.1 | 9.7 | 0.81 |
| Known cancer | 5.3 | 5.2 | 1.00 |
| Hereditary thrombophilia | 9.5 | 6.4 | 0.017 |
| Heart failure | 2.2 | 2.6 | 0.76 |
| Hemiparesis > 6 months | 1.1 | 1.2 | 1.00 |

*Patients with more than one event were counted only once. Age and weight were analyzed by the t-test, gender was analyzed by the χ^2 -test, all other parameters were analyzed by Fisher's exact test.

Table 2. Incidences of death, recurrent venous thromboembolism (VTE), major bleeding and the composite outcome during initial heparin treatment and the 6-month follow-up.

| Event and period of occurrence | LMWH (N=893) (%) | UFH (N=865) (%) | Relative risk reduction | Confidence Interval of relative risk | Fisher's Exact Test (2p) |
|--------------------------------|------------------------|-----------------------|----------------------------|--|--------------------------------|
| Recurrent VTE | | | | | |
| initial treatment | 1.6 | 2.1 | 0.75 | 0.38-1.50 | 0.48 |
| 6-month follow-up | 1.7 | 3.2 | 0.54 | 0.29-1.00 | 0.06 |
| total* | 3.1 | 5.1 | 0.62 | 0.39-0.98 | 0.04 |
| Death | | | | | |
| initial treatment | 0.1 | 0.3 | 0.32 | 0.04-2.76 | 0.37 |
| 6-month follow-up | 2.1 | 3.3 | 0.63 | 0.35-1.12 | 0.14 |
| total | 2.1 | 3.6 | 0.59 | 0.34-1.04 | 0.08 |
| Major bleeding | | | | | |
| initial treatment | 0.8 | 1.7 | 0.45 | 0.19-1.10 | 0.09 |
| 6-month follow-up | 1.1 | 1.8 | 0.65 | 0.29-1.44 | 0.32 |
| total* | 1.9 | 3.5 | 0.55 | 0.31-0.99 | 0.05 |
| Composite outcome | | | | | |
| initial treatment | 2.2 | 3.8 | 0.59 | 0.34-1.02 | 0.07 |
| 6-month follow-up | 4.2 | 6.9 | 0.61 | 0.41-0.91 | 0.02 |
| total* | 6.3 | 10.3 | 0.61 | 0.44-0.84 | 0.002 |

*: only one event was counted for the total incidence of events in those patients who had two events during the two treatment phases.

1362±374 IU/hr on day 1 and 1229±432 IU/hr on day 7. Vitamin K antagonist administration was started on day 4.3±2.9 in patients on unfractionated heparin and on day 7.8±1.8 in patients on LMWH.

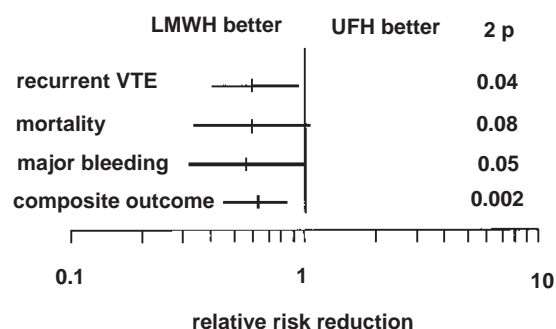


Figure 1. Relative risk reduction (RRR) and 95% confidence interval (CI) of recurrent venous thromboembolism (VTE), major hemorrhage, mortality and the composite outcome over 6 months after initial therapy of acute deep venous thrombosis with low molecular weight heparin or unfractionated heparin and oral anticoagulation during follow-up.

Primary outcome measure

Venous thromboembolism recurred during the total observation period in 3.1% and 5.1% in the patients allocated to LMWH and unfractionated heparin, respectively (relative risk reduction (RRR) 0.62, confidence interval (CI) 0.39 – 0.98, $2p=0.04$) (Figure 1). The incidences of venous thromboembolism during the initial and follow-up periods are given in Table 2. The higher number of patients with hereditary thrombophilia in the LMWH group does not explain the lower incidence of recurrent venous thromboembolism in these patients.

Other outcome measures

Major bleeding complications occurred in 1.9% and 3.5% of the patients in the LMWH and unfractionated heparin groups, respectively (RRR 0.55, CI 0.31 – 0.99, $2p=0.05$) (Figure 1). The incidences of major bleeds during the initial and follow-up periods are shown in Table 2.

Cochran-Mantel-Haenszel statistics and the Breslow-Day test for homogeneity of the odds ratios did not show significant differences between the studies regarding venous thromboembolism (Cochran-Mantel-Haenszel Test, $p=0.83$, Breslow-Day Test, $p=0.16$) or major bleeding ($p=0.63$ and $p=0.72$, respectively). The logistic regression analysis did not show significant effects of body-weight on venous thromboembolism ($p=0.56$) or major bleeding ($p=0.37$).

The total mortality rate was 2.1% and 3.6% in patients initially randomized to LMWH heparin and unfractionated heparin, respectively (RRR 0.59, CI 0.34 – 1.04, $2p=0.08$) (Figure 1). The frequencies

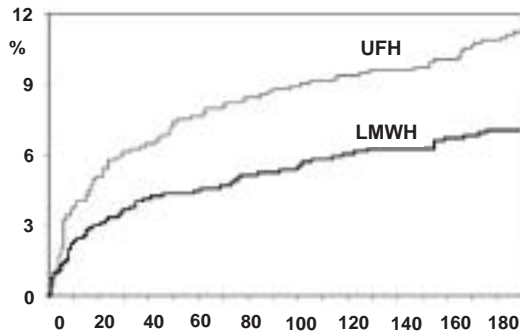


Figure 2. Cumulative incidence of composite outcome events during the study in patients randomized to initial therapy with unfractionated heparin (gray line) or low molecular weight heparin (black line).

during the initial and follow-up periods are given in Table 2. A statistical analysis of an influence of body weight on mortality was not performed, because a low body weight is related to age, multiple concomitant diseases and a poor general medical prognosis.

The composite outcome of recurrent venous thromboembolism, death, and major bleeding was observed in 6.3% of patients initially treated with

LMWH and in 10.3% of those receiving unfractionated heparin (RRR 0.61, CI 0.44 – 0.84, $2p=0.002$, Figure 1). The cumulative incidence is shown in Figure 2. The day of occurrence of the outcomes in the two treatment groups is given in Table 3.

Other findings

Recurrent venous thromboembolism and major bleeding were not correlated with the body weight of the patients in either treatment group during the initial or the follow-up period (*data not shown*). Thrombocytopenia without thromboembolism developed in 14 patients receiving LMWH and in 15 patients receiving unfractionated heparin and in no patient with recurrent thromboembolism.

Discussion

This pooled analysis of two independent studies demonstrates that the initial treatment of acute venous thromboembolism with one type of LMWH reduces the recurrence of venous thromboembolism during a follow-up period of 6 months. The production of low molecular weight heparins differs from that of unfractionated heparin, resulting in differences in pharmacological properties and effective doses for prophylaxis and treatment of throm-

Table 3. Day of occurrence of death, recurrent venous thromboembolism (VTE) or major hemorrhage during initial heparin therapy and the 6-month follow-up.

| | LMWH (N=893) | | UFH (N=865) | |
|-------------------------------------|-----------------|---|-----------------|---|
| | No. of patients | Days after start of therapy | No. of Patients | Days after start of therapy |
| Recurrent VTE (non-fatal) | | | | |
| Thrombosis | 13 | 6, 8, 9, 15, 15, 18, 23, 30, 35, 61, 93, 118, 155 | 20 | 4, 6, 6, 9, 10, 16, 17, 24, 24, 27, 29, 39, 50, 71, 85, 105, 116, 129, 166, 171 |
| Pulmonary embolism | 15 | 0, 1, 1, 1, 1, 1, 2, 2, 5, 8, 11, 41, 58, 76, 155 | 18 | 1, 1, 1, 2, 4, 4, 4, 5, 5, 6, 6, 7, 11, 15, 16, 17, 22, 187 |
| Total | 26 | | 35 | |
| Death | | | | |
| Pulmonary embolism | 2 | 7, 24 | 8 | 3, 18, 19, 30, 50, 165, 166, 174 |
| Hemorrhage | 1 | 155 | 2 | 6, 6 |
| Cancer | 8 | 14, 69, 73, 77, 100, 101, 102, 159 | 11 | 18, 22, 22, 43, 45, 57, 125, 153, 155, 167, 182 |
| Other | 8 | 21, 35, 38, 74, 84, 114, 123, 173 | 10 | 33, 49, 52, 63, 70, 88, 90, 97, 147, 153 |
| Total | 19 | | 31 | |
| Major hemorrhage (non-fatal) | | | | |
| Intracerebral | — | | 1 | 37 |
| Intra-abdominal | 1 | 5 | 7 | 2, 5, 6, 6, 6, 7, 11 |
| Gastrointestinal, urogenital | 9 | 1, 4, 8, 9, 16, 28, 29, 106, 128 | 12 | 24, 44, 48, 49, 62, 63, 78, 79, 101, 115, 170, 184 |
| Intramuscular | 3 | 8, 10, 33 | 6 | 1, 2, 2, 4, 6, 9 |
| Other | 3 | 46, 167, 176 | 2 | 3, 15 |
| Total | 16 | | 28 | |

boembolism.⁷ Accordingly, all LMWH preparations are regarded as individual compounds with individual efficacy, dosage and safety profiles. In fact, a summary analysis indicated differences between the odds ratios of incidences of recurrent venous thromboembolism and major hemorrhage over 3 to 6 months follow-up after initial treatment of venous thromboembolism with subcutaneous LMWH or intravenous unfractionated heparin.¹²

The only difference between the two studies considered here was the duration of the initial treatment with unfractionated heparin. With respect to recurrent events, the shorter treatment period with unfractionated heparin in one of the two studies may favor therapy with LMWH. However, prolonged therapy with subcutaneous LMWH did not improve the outcome of patients with acute venous thromboembolism.³ Thus, the shorter unfractionated heparin therapy in one of the two studies is unlikely to have influenced the present analysis indicating the superiority of LMWH. With regard to major hemorrhagic complications, no data are available in the literature to suggest that shortening the initial therapy of venous thromboembolism with unfractionated heparin by 3 to 4 days reduces the incidence of major bleeding. In contrast, a higher number of major bleeding complications has been reported during the initial therapy with unfractionated heparin than with LMWH.^{9-12,20,21} Thus, shortening therapy with unfractionated heparin should result in a lower incidence of major bleeding theoretically favoring therapy with unfractionated heparin rather than LMWH in the present analysis. We, therefore, believe that this difference in the design of the two studies does not unbalance the results or invalidate the conclusions of the combined analysis.

Most studies used body-weight-adjusted doses of LMWH for the treatment of symptomatic acute deep venous thrombosis. No studies have been performed to identify the optimal dose of LMWH to treat patients with acute deep vein thrombosis. The broader therapeutic window of LMWH has been suggested to be an advantage of this type of drug over unfractionated heparin.⁸ There are no definite arguments based on these considerations and the generated clinical data^{15,16,20,22} that patients cannot be treated with a fixed, body-weight-independent dose of a LMWH. Recently, other studies used only three doses³ or a fixed dose of LMWH²³ for the treatment of acute venous thromboembolism. These regimens were not found to be inferior, with respect to recurrent thromboembolism or major bleeding, to that of intravenous aPTT-adjusted unfractionated heparin. A fixed, body-weight independent dose of LMWH may be a limitation in individuals with a very low body weight.

The results of the present analysis demonstrate the better efficacy and safety over 6 months of a single LMWH rather than unfractionated heparin

for the treatment of acute deep venous thrombosis. Logistic regression analysis showed no dependence on body weight and medication for the effect on recurrent venous thromboembolism or major bleeding, which is important when using a fixed dose of the LMWH certoparin. The initial advantage of LMWH, regarding the incidence of recurrent venous thromboembolism as well as the composite outcome of recurrent venous thromboembolism, major bleeding and death, is maintained over 6 months. The treatment of patients with acute deep vein thrombosis can, therefore, be further simplified by using a fixed, body-weight-independent dose of LMWH.

References

- Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al. A comparison of low-molecular-weight heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996;334:677-81.
- Koopman MMW, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. *N Engl J Med* 1996;334:682-7.
- Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med* 2001;344:626-31.
- Hirsh J, Lee AY. How to diagnose and treat deep vein thrombosis. *Blood* 2002;99:3102-10.
- Young E, Wells P, Holloway S, Weitz J, Hirsh J. Ex-vivo and in-vitro evidence that low molecular weight heparins exhibit less binding to plasma proteins than unfractionated heparin. *Thromb Haemost* 1994;71:300-4.
- Harenberg J, Stehle G, Augustin J, Zimmermann R. Comparative human pharmacology of low molecular weight heparins. *Semin Thromb Haemost* 1989;15:414-23.
- Weitz JI. Low molecular weight heparins. *N Engl J Med* 1997;337:688-98.
- Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. Heparin and low-molecular-weight heparin. Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy and safety. *Chest* 2001;119:64-94.
- Leizorovicz A, Simonneau G, Decousus H, Boissel JP. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis. *Br Med J* 1994;309:299-304.
- Rocha E, Martinez-Gonzalez MA, Montes R, Panizo C. Do the low molecular weight heparins improve efficacy and safety of the treatment of deep venous thrombosis? A meta-analysis. *Haematologica* 2000;85:935-42.
- Van den Belt AGM, Prins MH, Lensing AW, Castro AA, Clark OAC, Atallah AN, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *The Cochrane Database Syst Rev* 2000;2:CD001100.
- Dolovich LR, Ginsberg JS, Douketis JD, Helbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med* 2000;160:181-8.
- van der Heijden JF, Prins MH, Büller HR. For the initial treatment of venous thromboembolism: are all low-molecular-weight heparin compounds the same? *Thromb Res* 2000;100:V121-V130.
- Wells PS, Rodger M, Forgie M, Anderson D, Kovacs M, Florack P, et al. A randomised trial comparing two low molecular weight heparins (LMWHs) for the outpatient treatment of DVT or PE. *Thromb Haemost* 2001; Suppl:968[abstract].
- Harenberg J, Schmidt JA, Kopenhagen K, Tolle A, Huisman MV, Büller HR. Fixed-dose, body weight-independent subcutaneous

- LMW heparin versus adjusted dose unfractionated intravenous heparin in the initial treatment of proximal venous thrombosis. EASTERN Investigators. *Thromb Haemost* 2000;83:652-6.
16. Riess H, Koppenhagen K, Tolle A, Kemkes-Matthes B, Grave M, Patek F, et al. 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. The TH-4 Study Group. *Thromb Haemost* 2003;90:252-9.
 17. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg* 1972;104:134-44.
 18. Wells PS, Lensing AWA, Davidson BL, Prins MH, Hirsh J. Accuracy of ultrasound for diagnosis of deep venous thrombosis in asymptomatic patients after orthopedic surgery. A meta-analysis. *Ann Int Med* 1995;122:47-53.
 19. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA* 1990;263:2753-9.
 20. Kirchmaier CM, Lindhoff-Last E, Rubesam D, Scharrer I, Vigh Z, Mosch G, et al. Regression of deep vein thrombosis by i.v.-administration of a low molecular weight heparin - results of a pilot study. *Thromb Res* 1994;73:337-48.
 21. Harenberg J, Huisman MV, Tolle AR, Breddin HK, Kirchmaier CM. Reduction in thrombus extension and clinical endpoints in patients after initial treatment for deep vein thrombosis with fixed-dose body weight-independent low-molecular-weight heparin Certoparin. *Semin Thromb Hemost* 2001;27:513-8.
 22. Harenberg J, Huck K, Bratsch H, Stehle G, Dempfle CE, Mall K, et al. Therapeutic application of subcutaneous low-molecular-weight heparin in acute venous thrombosis. *Haemostasis* 1990;20 Suppl:205-19.
 23. Monreal M, Büller H, Lensing AW, Bonet M, Roncales J, Muchart J, et al. Should patients with deep vein thrombosis alone be treated as those with concomitant asymptomatic pulmonary embolism? A prospective study. *Thromb Haemost* 2002;88:938-42.

Pre-publication Report & Outcomes of Peer Review

Contributions

JH and HR were sub-investigators of studies TH3 and TH4. JH, HB, MH were the writing committee of the publication. JH, HR, JB and GW were responsible for setting up the study protocol. JB and GW were responsible for the organization of the study.

We greatly appreciate the statistical evaluation of Helmut Bachmann and the participation of the study centers, listed in the appendices of the relevant publications, in the two clinical trials.

Funding

The clinical trials were supported by an educational grant from Novartis Pharma GmbH, Nuremberg, Germany.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Vicente Vicente, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Professor Vicente and the Editors. Manuscript received June 16, 2003; accepted August 8, 2003.

In the following paragraphs, Professor Vicente summarizes the peer-review process and its outcomes.

What is already known on this topic

Several studies have indicated a better efficacy and safety of subcutaneous body-weight adjusted low-molecular weight heparins as compared to intravenous unfractionated heparin for the initial treatment of patients with acute DVT.

What this study adds

This clinical study indicates that the efficacy and safety of a fixed dose of low-molecular weight heparin for treatment of acute DVT are superior to those of unfractionated heparin over 6 months.

Caveats

No studies are available to identify the optimal dose of low-molecular weight heparin to treat patients with DVT. Subsequently, a broader therapeutic window for low-molecular weight heparin has been suggested as an advantage over unfractionated heparin.