

Prevention of Deep Vein Thrombosis after Hip Replacement

Comparison between Two Low-molecular-weight Heparins, Tinzaparin and Enoxaparin

André Planès¹, Meyer M. Samama², Anthonie W. A. Lensing³, Harry R. Büller³, Jeanne Barre⁴, Nicole Vochelle⁴, Bertrand Beau⁵

From ¹Clinique Radio-Chirurgicale du Mail, La Rochelle, France, ²Hôpital Hôtel Dieu, Paris, France, ³Academic Medical Center, Amsterdam, The Netherlands; ⁴Hôpital Robert Debré, Reims, France, ⁵LEO Laboratories, Saint Quentin en Yvelines, France

Summary

Consecutive patients undergoing total hip replacement in 43 centres were randomly assigned to receive blindly either enoxaparin (40 mg) or tinzaparin (4,500 anti-Factor IU Xa), as once daily subcutaneous injections. The first injection was administered 12 h preoperatively. Efficacy was assessed by bilateral venography performed 12-14 days postoperatively. Efficacy and safety were blindly and centrally adjudicated. Among the 499 patients included, 440 had a venogram. The total incidence of DVTs was 44 (20.1%) of the 219 patients of the enoxaparin group and 48 (21.7%) of the 221 patients of the tinzaparin group. The upper limit of the 80% confidence interval of the difference between the two treatment groups was less than 5.0%. Therefore according to the protocol's specifications equivalence was shown. Proximal DVTs occurred in 10.5% of the enoxaparin group (23 patients) and in 9.5% (21 patients) of the tinzaparin group. No overt major bleeding was observed. One patient in the enoxaparin group developed severe thrombocytopenia and died. The LMWH tinzaparin appears clinically to be as effective and safe as enoxaparin in the prophylaxis of deep vein thrombosis after total hip replacement, at the doses used and under the conditions of this study.

Introduction

Low-molecular-weight heparins (LMWHs) share two main advantages over unfractionated heparin (UFH): better bioavailability and longer half-life after subcutaneous (s.c.) administration (1, 2). The results of successive trials and metaanalyses (3-5) have demonstrated their superiority over classical UFH prophylaxis in the prevention of deep-vein thrombosis (DVT) in orthopaedic surgery. However, there are major chemical and pharmacological differences between the various available LMWH preparations. Thus, they are considered as different entities and regulatory authorities have required clinical assessment of each LMWH for every indication for which approval is sought. Tinzaparin (marketed as Innohep[®]), is obtained by enzymatic degradation of porcine heparin and has been investigated in total hip replacement (THR) with a bodyweight adjusted dosage. Mätzsch et al., used a daily dosage of 50 anti-Factor Xa IU/kg begun two hours before surgery (the mean dose administered was 3,635 anti-Factor IU Xa/day)

versus dextran 70 and demonstrated that tinzaparin had statistically significant greater efficacy ($p = 0.04$) than dextran (6). Lassen et al. used the same dosage, also on a once daily basis, with a placebo comparator (7). They observed 32 percent of DVTs in the tinzaparin group versus 46 percent in the placebo group ($p = 0.02$). They estimated that the suboptimal efficacy observed in this study may have been due to a dose of tinzaparin which was too low. In a study of total hip replacement (THR) prophylaxis, Hull et al., used an increased dosage of 75 anti-Factor IU Xa/kg bodyweight once daily s.c. (a mean dose of approximately 5,250 anti-Factor IU Xa), starting 18 to 24 hours after surgery. In this study 398 patients received tinzaparin and 397 warfarin, adjusted daily to the International Normalized Ratio target range (8). The observed incidence of venographically detected DVTs was 21 percent in the LMWH group versus 23 percent in the warfarin group (NS), whereas the incidence of major bleeding events was higher in the LMWH group (2.8%) than in the warfarin patients (1.5% - NS). The results of these studies led us to select an intermediate fixed dosage of 4,500 anti-Factor IU Xa. We think it is preferable to use a fixed dose rather than a cumbersome and less reliable bodyweight adjusted dosage. In France and EU, the reference LMWH for prophylaxis after orthopaedic surgery is the widely investigated enoxaparin given at the fixed dose of 40 mg once daily s.c. (= 4,000 anti-Factor Xa IU) initiated either pre- or postoperatively (9-14). The present trial was performed to compare the efficacy and safety of tinzaparin and enoxaparin in a double-blind equivalence trial.

Methods

Study Design

This study was a prospective, randomized, double-blind clinical trial comparing two parallel groups of patients receiving either enoxaparin (Rhone Poulenc Rorer, France) or tinzaparin (Leo, Denmark) given once daily to patients undergoing THR. Forty three centres in France participated in the trial between March and October 1994. The protocol was approved by the Consultative Committee for Protection of Individuals involved in Medical Research, of the Poitou-Charentes district, and by the National Health Authorities.

Patients

Consecutive eligible patients, 40 years of age or older, weighing between 50 kg and 90 kg, scheduled to undergo primary THR, who gave written informed consent, were enrolled in the study. Patients who received general anaesthesia were eligible if they had none of the following: allergy to heparin, to iodine or radiopaque contrast medium; acquired or hereditary haemostatic disorders; disorders contraindicating anticoagulant prophylaxis; severe hepatic or renal failure; severe or malignant hypertension; a history of DVT or

Correspondence to: Dr. A. Planès, Clinique Radio-Chirurgicale du Mail, 96 Allées du Mail, 17028 La Rochelle Cedex, France - Tel.: (33) 5 46 01 31 39; FAX Number: (33) 5 46 01 39 19

Supported by LEO Laboratories, France

pulmonary embolism (PE) within the previous 6 months; myocardial infarction or stroke within the previous 6 months; revision or conversion hip surgery or primary hip arthroplasty of the opposite hip performed less than 3 months previously; advanced cancer; pregnancy. A stratification by study centre was performed by a computer generated randomization schedule balanced by blocks of four.

Treatment Regimens

Once daily the patients received subcutaneously either enoxaparin, 40 mg (4,000 anti-Factor IU Xa), or tinzaparin, 4,500 anti-Factor IU Xa. Both LMWHs were dispensed in identical prefilled syringes of 0.40 ml. Treatment was begun 12 h preoperatively, followed by a second injection 12 h postoperatively, and then at the same time on a once daily basis. Each patient entering the trial received a box containing sufficient quantity of the allocated treatment to last 15 days. The use of drugs containing acetylsalicylic acid was prohibited during the study, and the use of nonsteroidal antiinflammatory drugs was strongly discouraged. Ticlopidin, if used, had to have been stopped at least 15 days prior to surgery.

Surveillance and Follow-up

Pre- and postoperative bleeding was measured, as was the need for transfusions. Great variation was observed between centres regarding the measures used to minimize transfusion requirements of homologous blood and no strict policy of transfusion could be established. Some centres transfused autologous blood donated prior to surgery, others used a preoperative hemodilution, others a salvage of the patient's blood by use of cell-saver or special suction drainage (hemovac). As all these different methods were utilised to reduce the need for transfusion, it was finally decided to concentrate the analysis on transfusion of homologous blood. The protocol stipulated that during the trial each centre should be consistent in applying the same method of minimising the need for transfusion to each patient at that centre. All patients were examined daily. A bleeding episode was classified as major if it was overt and associated with either a fall in hemoglobin level of 2 g/dl or more, or a need for transfusion of two or more units of blood, or if it was retroperitoneal, intracranial or intra-ocular. Bleeding was defined as minor if it was overt but did not meet the other criteria for major bleeding. Wounds were examined and bruises, haematomas, need for surgical intervention, infection, and length of hospital stay were documented. Patients underwent bilateral venography of the lower limbs 12-14 days after surgery, unless overt symptoms of DVT or PE required an earlier, diagnostic, venogram. Venograms were interpreted locally, to allow for any intervention necessary, and then by a centralised assessment by an independent panel of experts blind to treatment allocation and the local assessment

results. A DVT was diagnosed if a constant intraluminal filling defect was present in more than one projection. Non-opacification of a vein, or a segment thereof, despite repeated injection of contrast medium, or on venograms made at different time points, was also considered to indicate venous thrombosis. DVTs were classified as distal if below the trifurcation of the calf veins, or proximal if they occurred in the popliteal, femoral or iliac veins or in the vena cava. When a patient presented both proximal and distal DVTs, this was classified as being proximal. When PE was clinically suspected, it required objective confirmation by lung scan or pulmonary angiography. A central Safety Committee reported blindly on the compliance to the protocol, and on the bleeding episodes. The decision whether to use post-discharge prophylaxis or to treat detected DVTs was left at the discretion of each centre and the trial ended with the venographic examination.

Sample Size Calculation and Statistical Analysis

The primary endpoint was the total rate of DVT diagnosed as defined previously. As this study's objective was to demonstrate equivalence between the two LMWHs, the aim was to prove that tinzaparin was not less effective than enoxaparin. Hence the risk of a type I error was one sided and at a level of 20%, as was that of the type II error. The equivalence interval was defined such that the upper confidence level of the absolute difference in DVT rates would not exceed 5%. The sample size was calculated on the basis of an expected rate of 10% in the enoxaparin group and the target was 408 patients (204 in each group). Efficacy was assessed by intention-to-treat analysis. A secondary criterion of efficacy was the rate of proximal DVTs. Tolerance was assessed by intention-to-treat analysis on all patients entered in the trial with the usual two-tailed type I error of 5%.

Results

Four hundred and ninety nine consecutive patients scheduled for elective hip replacement were enrolled in the study. The characteristics of the treatment groups were similar at entry to the study (Table 1). Two hundred and forty eight were assigned to receive enoxaparin and two hundred and fifty one to tinzaparin. Three patients received only one injection of LMWH and were excluded by the investigator before surgery for various reasons. Twenty eight patients in each group did not have venograms. This left 440 patients (88%) who had a venographic assessment, 219 received enoxaparin and 221 tinzaparin. The two groups remained comparable with regard to baseline characteristics (data not shown). The mean (\pm SD) duration of treatment was 12 + 2 days in both groups.

Efficacy Analysis

The overall rate of DVT was 20.1 percent in the enoxaparin group (44/219) and 21.7 percent in the tinzaparin group (48/221) (Table 2). In the intention-to-treat analysis, the absolute risk difference was 1.6% (95% CI: -6.0 to 9.2%). The upper limit of the 80% confidence interval of this difference was 4.9%, within the limit defined in the protocol to conclude equivalence as regards the main criterion of efficacy. The observed rate of proximal DVT in the enoxaparin group was 10.5% (23/219) and 9.5% (21/221) in the tinzaparin group (NS). Two documented symptomatic non fatal PE, one in each group, were observed. Among the 92 DVTs, 26 (13 in each group) were exclusively on the nonoperative side and 11 were bilateral (3 in the enoxaparin group and 8 in the tinzaparin group). Only 5 of the 92 DVTs were clinically symptomatic (3 in the enoxaparin group and 2 in the tinzaparin group). Usual physical methods including elastic bandaging of the legs, elevation of the foot of the bed, had been recommended but were not uniformly applied. Of the 320 patients for whom these recommenda-

Table 1 Baseline characteristics of the study groups

Characteristic	Enoxaparin group (N = 248)	Tinzaparin group (N = 251)
Age (yr) mean (\pm SD)	64 \pm 11	65 \pm 11
Weight (kg) mean (\pm SD)	71 \pm 13	71 \pm 11
no. of patients (%)		
Male sex	111 (45)	108 (43)
Venous thromboembolism history	21 (9)	28 (11)
Reasons for hip replacement*		
- osteoarthritis	216 (87)	223 (89)
- congenital dysplasia	19 (8)	16 (6)
- avascular necrosis	15 (6)	13 (5)
- sequelae of trauma	9 (4)	6 (2)
- rheumatoid arthritis	5 (2)	3 (1)
- others	8 (3)	3 (1)
Operative time (min) mean (\pm SD)	89 \pm 44	87 \pm 39
Anesthetic time (min) mean (\pm SD)	161 \pm 26	159 \pm 61

* More than one reason for some patients.

tions were followed, 56 (17.5%) had a DVT, among the 120 patients with no specific physical prevention, the corresponding number was 36 (30.0%) (p = 0.004). However, this did not influence our results since physical methods were used to the same extent in both treatment groups, (tinzaparin group: 71.5%, enoxaparin group: 74.0%). For the 223 patients with venograms and weighing 71 kg (median weight of the population) or more, the rate of DVTs reached 20.6%. For the 217 patients below 71 kg, this rate was 21.2%. These figures were similar in both groups. For the 59 patients with venograms and for whom Body Mass Index (BMI) was 30 or above, the rate of DVTs was 27.1%. For the 381 patients with BMI below 30, this rate was 20.0% (p = 0.20). These figures were similar across both groups. Ten centres recruited half of the patients (247/499). The rate of DVTs in these centres was comparable to the rate observed in the other 33 centres (19.5% and 22.4% respectively).

Safety Analysis

A 68-year-old woman on enoxaparin, without medical history, developed a dramatic heparin induced thrombocytopenia (HIT) and severe thrombocytopenia ($40 \times 10^9/l$) on the 9th postoperative day. This patient died 2 days later from irreversible aseptic shock from adrenal hemorrhagic necrosis and renal/pulmonary venous thrombosis which were discovered at autopsy. HIT antibody was detected by the ELISA test on the 6th postoperative day which was three days before the effective decrease in platelet count. The platelet count of approximately $200 \times 10^9/l$ on the 6th day was similar to the platelet count on the first postoperative day. On the 9th day, at the nadir of thrombocytopenia, the ELISA test was strongly positive. More details may be found in reference (15). Pre- and postoperatively, no difference was observed between the two groups as regards immediate bleeding tendency, assessed by the total blood loss in the two groups. Homologous blood requirements were similar in both groups. All major bleeds were observed at the wound site (4 patients in the enoxaparin group and 2 in the tinzaparin group). Two patients required further surgery and 3 others were excluded from the trial by the investigator. Minor bleeds were found in 34 patients: 21 in the enoxaparin group versus 13 in the tinzaparin group (p = 0.09).

Anti-Factor Xa and anti-Factor IIa Levels

These measurements were determined in a central laboratory (Dr. Bara) in a group of patients at peak level, i.e., 3-4 h after injection (Table 3). A statistically significant higher anti-Factor IIa level was found in the tinzaparin group at each assessment. On the other hand, a significant higher level of anti-Factor Xa was found in the enoxaparin

*Table 3 Anti-Factor IIa and Xa levels (mean + SD, IU)**

Day of sample	Enoxaparin Group		Tinzaparin Group	
	Anti IIa	Anti Xa	Anti IIa	Anti Xa
Day 1 or 2 (n = 108)	0.39 ± 0.05	0.55 ± 0.15**	0.12 ± 0.06**	0.17 ± 0.13
Day 5 or 6 (n = 161)	0.49 ± 0.05	0.59 ± 0.17**	0.11 ± 0.05**	0.18 ± 0.12
Discharge day (n = 83)	0.39 ± 0.05	0.58 ± 0.19**	0.12 ± 0.06**	0.40 ± 0.15

* Anti-Factor IIa and anti-Factor Xa levels were blindly and centrally assessed by ELISA method on samples collected 3-4 hours after injection (peak level).
 ** Anti-Factor IIa is significantly higher in the tinzaparin group and Anti-Factor Xa in the enoxaparin group. P values < 0.001 (analysis of variance).

group at each assessment. These results will be reported in details in a separate publication.

Discussion

This doubleblind study showed that the rate of DVT assessed by bilateral venography was equivalent for both LMWH regimens, enoxaparin or tinzaparin, given subcutaneously at a fixed dose (independent of body weight), started 12 h before surgery. The overall incidence of DVTs was 20.1% (intention-to-treat analysis) in the enoxaparin group. The corresponding figure was 21.7% in the tinzaparin group. The rate of proximal DVTs was 10.5% (enoxaparin group) and 9.5% (tinzaparin group). The efficacy results obtained with LMWHs in the prophylaxis of DVT after orthopaedic surgery vary to a great extent, which may be due to differences in the LMWHs, the doses used, the methods of DVT assessment and the centres in which the trial were conducted. We have described this wide discrepancy in trials performed with tinzaparin but it has also been observed with enoxaparin. Incidences of total DVT varied from 12.5%, 6.5%, 6.5% to 17%, 14%, 9%, 25.5% in trials (9-14) respectively. Incidences of proximal DVT varied from 7.5%, 1.8%, 6%, 6%, 6% and 7.5% in the same trials. If the variable rates observed with tinzaparin may be related to different dosages, this is not the case with enoxaparin which was used in all these trials at the same dosage of 40 mg/day. These wide variations have been investigated and various factors have been described: interobserver variability in the interpretation of venograms (which may be improved with long leg films and good filling of the venous system with contrast media), centre and country effects, criteria used for radiological diagnosis of DVT, use of bilateral venography (in our study 28% of the DVTs were located exclusively on the nonoperative side) (8, 14, 16-19). However, the objective of this study was not to determine the absolute efficacy of the LMWHs as it could have been done in a placebo controlled trial, but rather to compare the efficacy and the safety of the two LMWHs administered at specified and fixed dosages. Limited data are available concerning a direct comparison of two LMWHs (13). This could become more frequent for registration purposes when a given drug has become the reference product, as it has been the case for enoxaparin in France and EU (13, 14). The advantages of performing a trial in a large number of centres are to accurately reflect clinical practice and to avoid the biases of recruitment in limited, specialised centres. In addition to the LMWH treatment, the use of physical prevention methods resulted in a significant reduction in incidence venous thrombosis. However, this did not influence the final outcome of the study since these strategies were used to the same extent in both groups.

Table 2 Frequency and distribution of thrombosis (central reading of venograms)

Result	Enoxaparin group (N = 219)	Tinzaparin group (N = 221)
	no. of patients (%)	
Bilateral normal venogram	166 (75.7)	154 (69.7)
Unilateral normal venogram	3 (1.4)	2 (0.9)
Inadequate negative venogram	12 (5.5)	17 (7.7)
Deep vein thrombosis	41 (18.7)	48 (21.7)
- proximal	23 (10.5)	21 (9.5)
- distal	21 (9.6)	27 (12.2)

Body weight did not influence the risk for DVT since the incidence of DVT was similar in patients above and below the median weight. Furthermore, the mean weight of the patients with DVT was identical to that in those without DVT. Concerning obesity, a risk factor for thromboembolism, our data indicate only a nonsignificant trend, in both groups. In the obese patients, defined as a Body Mass Index of 30 or above, the overall DVT incidence was 27% versus only 20% in the nonobese patients ($p = 0.2$). These figures are in favour of the administration of LMWHs, in the prophylaxis of DVT, at fixed doses, independent of body weight. Clinical efficacy and safety of both LMWHs were satisfactory and similar to previously reported results. Interestingly although similar doses expressed in IU of anti-Xa were administered, anti-Xa plasma levels were significantly higher with enoxaparin than with tinzaparin. However, these differences could be due to different pharmacokinetics of the two drugs. Despite regular platelet counts a fatal case of thrombocytopenia occurred. Whatever the exact advantages of LMWHs in comparison with unfractionated heparin concerning the risk of HIT, this risk remains and monitoring of platelet counts may be indicated in the prophylactic therapies (20, 21). In conclusion, in this trial of prophylaxis of DVT after orthopaedic surgery, tinzaparin 4,500 IU Xa s.c. once daily was equivalent to enoxaparin 40 mg s.c. once daily.

Appendix

Investigators in this study were as follows:

The principal investigator was: A. Planès, Clinique du Mail, La Rochelle, France.

The members of the Safety Committee were: Meyer M. Samama, Hôtel Dieu, Paris, France; Jeanne Barré, Hôpital Robert Debré, Reims, France; Jacques Barsotti, Hôpital Trousseau, Tours, France. *The Steering Monitor was:* Mickaël R. Lassen, Danish Clinical Research, Aalborg, Denmark. *The central assessment of anti-IIa and anti-Xa levels was done by:* Lucienne Bara, Institut Pierre et Marie Curie, Paris. *The central assessment of venograms was done by:* Jan W. ten Cate, Harry R. Büller, Anthonie W. A. Lensing, Academic Medical Centre, Amsterdam, The Netherlands. *The investigators (all in France) were:* A. Carnec (Saint Sauve), M. Delecroix (Lille), J-P. Levai (Clermont-Ferrand), M. Kerboull (Paris), A. Rerolle (Chenove), N. Dufeu (Paris), J-L. Chatelan (Libourne), C. Vielpeau (Caen), P. Tramond (Libourne), M. Lavy (Saint Etienne), F. Trepo (Lyon), D. Goutallier (Créteil), N. Clermont (Lyon), J-P. Moulinie (Paris), D. Dogimont (Bordeaux), X. Normand (Chamalières), Ph. Rosset (Tours), G. Utheza (Toulouse), Ch. Mabit (Limoges), J-P. Clarac (Poitiers), J. Aubriot (Caen), D. Molé (Nancy), A. Le Rebeller (Bordeaux), K. Lobjoit (Saint Germain en Laye), J-P. Carret (Caluire), Ph. Beaufiles (Le Chesnay), B. Robine (Le Chesnay), Cl. Argenson (Nice), F. Volot (Dijon), J-F. Olivero (Paris), B. Lenoir (Saint Mandé), J-P. Delagoutte (Nancy), J. Preault (Bar le Duc), E. Dissez (Pessac), J. Tabutin (Cannes), P. Athtar (Perpignan), G. Bousquet (Saint Etienne), E. Vassort (Grenoble), J-F. Kouvalchouk (Suresnes), A. Apoil/A. Lienhart (Paris), Ch. Vidil (Saint Martin d'Hyères), B. Tayon (Pontoise). We are indebted to Pr. J. W. ten Cate and to Dr. J. Stinson (Dublin) for reviewing the manuscript.

References

- Hirsh J, Levine MN. Low-molecular-weight heparin. *Blood* 1992; 79, 1: 1-17.
- Barrowcliffe TW, Johnson EA, Thomas DP. Low molecular weight heparin. Eds John Wiley, Chichester 1992.
- Nurmohamed MT, Rosendaal FR, Büller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet* 1992; 340: 152-6.
- Leizorovicz A, Haugh MC, Chapuis FR, et al. Low-molecular-weight heparin in prevention of perioperative thrombosis. *BMJ* 1992; 305: 913-20.
- Jorgensen LN, Wille-Jorgensen P, Hauch O. Prophylaxis of postoperative thromboembolism with low molecular weight heparins. *Br J Surg* 1993; 80: 689-704.
- Mätzsch T, Bergqvist D, Fredin H, et al. Comparison of the thromboprophylactic effect of a low-molecular-weight heparin versus dextran in total hip replacement. *Thromb Haemorrh Disorders*, 1991; 3 (1): 25-9.
- Lassen MR, Borris LC, Christiansen HM, et al. Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. *Acta Orthop Scand* 1991; 62 (1): 33-8.
- Hull R, Raskob G, Pineo G, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med* 1993; 329: 1370-6.
- Planes A, Vochelle N, Mazas F, et al. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low-molecular-weight heparin in patients undergoing total hip replacement. *Thromb Haemost* 1988; 60: 407-10.
- The Danish Enoxaparin Study Group. Low-molecular-weight heparin (Enoxaparin) vs Dextran 70: the prevention of postoperative deep vein thrombosis after total hip replacement. *Arch Intern Med* 1991; 151: 1621-4.
- Planes A, Vochelle N, Fagola M et al. Prevention of deep vein thrombosis after total hip replacement. the effect of low-molecular-weight heparin with spinal and general anaesthesia. *J Bone Joint Surg* 1991; 73 B: 418-22.
- Spiro TE, Johnson GJ, Christie MJ, et al. Efficacy and safety of enoxaparin to prevent deep venous thrombosis after hip replacement surgery. *Ann Intern Med* 1994; 121, 2: 81-9.
- Planes A. Comparison of antithrombotic efficacy and haemorrhagic side-effects of Clivarin versus enoxaparin in patients undergoing total hip replacement surgery. *Blood Coagul Fibrinolysis* 1993; 4, suppl 1, S33-5.
- Eriksson BI, Wille-Jorgensen P, Kälebo P et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med* 1997; 337: 1329-35.
- Elalamy I, Potevin F, Lecrubier C, et al. A fatal low-molecular-weight heparin associated thrombocytopenia after hip surgery: possible usefulness of PF4-heparin Elisa test. *Blood Coagul and Fibrinolysis* 1996; 7: 665-71.
- Bounameaux H, Prins TR, Schmitt HE et al. Venography of the lower limbs. Pitfalls of the diagnostic standard. *Invest Radiol* 1992; 27: 1009-11.
- Lensing AWA, Büller HR, Prandoni P et al. Contrast venography, the gold standard for the diagnosis of deep-vein thrombosis: improvement in observer agreement. *Thromb Haemost* 1992; 67: 8-12.
- Wille-Jorgensen P, Borris L, Jorgensen N et al. Phlebography as the gold standard in thromboprophylactic studies? A multicenter interobserver variation study. *Acta Radiologica* 1992; 33: 24-8.
- Couson F, Bounameaux C, Didier D et al. Influence of variability of interpretation of contrast venography for screening of postoperative deep venous thrombosis on the results of a thromboprophylactic study. *Thromb Haemost* 1993; 70 (4): 573-5.
- Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; 332: 1330-5.
- Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards a consensus. *Thromb Haemost* 1998; 79: 1-7.

Received December 4, 1997 Accepted after resubmission September 16, 1998