Low-molecular weight heparin in the treatment of patients with venous thromboembolism: the Columbus Investigators

Büller, H.R.; Gent, M.; Gallus, A.S.; Ginsberg, J.; Prins, M.H.; Baildon, R.; ten Cate, J.W.

Publication date
1997

Published in
The New England journal of medicine

The New England Journal of Medicine

VOLUME 337 SEPTEMBER 4, 1997 NUMBER 10

LOW-MOLECULAR-WEIGHT HEPARIN IN THE TREATMENT OF PATIENTS WITH VENOUS THROMBOEMBOLISM

THE COLUMBUS INVESTIGATORS*

ABSTRACT

Background Low-molecular-weight heparin is known to be safe and effective for the initial treatment of patients with proximal deep-vein thrombosis. However, its application to patients with pulmonary embolism or previous episodes of thromboembolism has not been studied.

Methods We randomly assigned 1021 patients with symptomatic venous thromboembolism to fixed-dose, subcutaneous low-molecular-weight heparin (reviparin sodium) or adjusted-dose, intravenous unfractionated heparin. Oral anticoagulant therapy with a coumarin derivative was started concomitantly and continued for 12 weeks. Approximately one third of the patients had associated pulmonary embolism. The outcome events studied over the 12 weeks were symptomatic recurrent venous thromboembolism, major bleeding, and death. We sought to determine whether low-molecular-weight heparin is at least equivalent to unfractionated heparin in patients with venous thromboembolism.

Results Twenty-seven of the 510 patients assigned to low-molecular-weight heparin (5.3 percent) had recurrent thromboembolic events, as compared with 25 of the 511 patients assigned to unfractionated heparin (4.9 percent). The difference of 0.4 percentage point indicates that the two therapies have equivalent value according to our predetermined definition of equivalence. Sixteen patients assigned to low-molecular-weight heparin (3.1 percent) and 12 patients assigned to unfractionated heparin (2.3 percent) had episodes of major bleeding ($P = 0.63$), and the mortality rates in the two groups were 7.1 percent and 7.6 percent, respectively ($P = 0.89$).

Conclusions Fixed-dose, subcutaneous low-molecular-weight heparin is as effective and safe as adjusted-dose, intravenous unfractionated heparin for the initial management of venous thromboembolism, regardless of whether the patient has pulmonary embolism or a history of venous thromboembolism. (N Engl J Med 1997;337:657-62.)

IN Western countries, each year 2 to 4 persons per 1000 require anticoagulant therapy for symptomatic deep-vein thrombosis or pulmonary embolism.[1-3] Although deep-vein thrombosis and pulmonary embolism were previously regarded as separate clinical entities, there is good evidence that they are expressions of a single disease process — namely, venous thromboembolism.[4-6]

Until recently, the standard treatment of patients with venous thromboembolism was hospital admission, with unfractionated heparin given by intravenous infusion for 5 to 10 days, followed by oral anticoagulant therapy for at least 3 months.[7,8] Because patients vary widely in their anticoagulant response to unfractionated heparin, frequent laboratory monitoring with appropriate dose adjustment is needed to keep their level of anticoagulation in the therapeutic range. In contrast, the longer half-life of low-molecular-weight heparins and the more predictable anticoagulant response make them suitable for subcutaneous administration without laboratory monitoring.

Initial trials in hospitalized patients with proximal deep-vein thrombosis showed that low-molecular-weight heparin in a dose determined by body weight alone is at least as effective and safe as unfractionated heparin.[9,10] Two further recent trials have had similar results when low-molecular-weight heparin was given mainly on an outpatient basis to suitable patients with proximal deep-vein thrombosis.[11,12] However, using due caution, these studies excluded patients with symptoms of pulmonary embolism and some

The Writing Committee of the Columbus Study (H.R. Büller, M. Gent, A.S. Gallus, J. Ginsberg, M.H. Prins, and R. Baildon) takes responsibility for the content of this article. Address reprint requests to Professor J.W. ten Cate, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam Zuid-oost, the Netherlands.

*The institutions and investigators participating in the study are listed in the Appendix.

patients with a history of venous thromboembolism, because such patients are thought to have more serious thromboembolic disease. Before the widespread use of low-molecular-weight heparin is recommended, the effectiveness of these agents in treating the full spectrum of patients with venous thromboembolism must be confirmed.

We report the results of a large, open, international, randomized clinical trial designed to determine whether fixed-dose, subcutaneous low-molecular-weight heparin and adjusted-dose, continuous intravenous unfractionated heparin have at least equivalent efficacy in unselected patients with symptomatic venous thromboembolism. We studied the clinical outcomes of recurrent venous thromboembolism, hemorrhage, and death during 12 weeks of follow-up, with blinded validation of outcome events by a central adjudication committee.

METHODS

Study Patients

Consecutive patients with acute, symptomatic deep-vein thrombosis, pulmonary embolism, or both who were considered to require antithrombotic therapy were eligible for the study. The symptomatic deep-vein thrombosis could be limited to the calf or could involve the popliteal vein or a more proximal vein; the diagnosis had to be documented by ultrasonography or venography. Clinically suspected pulmonary embolism was confirmed by ventilation–perfusion lung scanning that showed a high probability of pulmonary embolism or by pulmonary angiography or, if lung scanning was nondiagnostic, by the demonstration of deep-vein thrombosis on compression ultrasonography or venography.[5,6]

Patients who met these criteria for inclusion were ineligible for the study if they had received therapeutic doses of low-molecular-weight heparin, unfractionated heparin, or oral anticoagulant therapy for more than 24 hours; if anticoagulant therapy was contraindicated; if thrombolytic therapy was planned; if they had had gastrointestinal bleeding in the preceding 14 days; if they had undergone surgery requiring anesthesia within the previous 3 days; if they had had a stroke in the preceding 10 days; if the platelet count was less than 100,000 per cubic millimeter; if they weighed less than 35 kg; if they were less than 18 years old; if they had a documented pregnancy or had childbearing potential but were not using adequate contraception; or if they were in a location that made follow-up difficult. Patients were enrolled whether venous thromboembolism developed in the hospital or while the patients were outpatients. The feasibility of treatment at home was not considered in assessing eligibility. After the patient gave informed consent, randomization (stratified according to whether the patient presented with deep-vein thrombosis only or with pulmonary embolism, and also stratified according to clinical center) was performed with a computer algorithm and the use of a central 24-hour telephone service that recorded information on the patient before the treatment assignment was disclosed. The study protocol was approved by the institutional review boards of all the clinical centers.

Treatment Regimens

The patients randomly assigned to low-molecular-weight heparin received reviparin sodium (Clivarin, Knoll, Ludwigshafen, Germany), administered subcutaneously in the following fixed doses: 6300 anti–factor Xa units twice daily (according to the first international standard for low-molecular-weight heparin), for patients weighing more than 60 kg; 4200 units twice daily, for patients weighing 46 to 60 kg; and 3500 units twice daily, for patients weighing 35 to 45 kg. Patients could be treated at home, but the decision to do so was left to the treating physician. Patients who received some or all of their treatment at home were instructed by a nurse in the method of self-injection. When self-administration was not feasible, the injections were given by a relative or a nurse.

The patients randomly assigned to unfractionated heparin were treated in the hospital. They received an intravenous bolus injection of 5000 IU (Liquemin, Roche, Basel, Switzerland), followed by a dose of 1250 IU per hour given by continuous intravenous infusion and adjusted according to a nomogram.[13] In practice, the clinical centers used an activated partial-thromboplastin time of 60 to 85 seconds as a target value or a fixed ratio of 1.5 to 2.5 times a control value.[8] These tests were performed 6 to 12 hours after the start of treatment or 6 to 12 hours after a subtherapeutic activated partial-thromboplastin time was measured, and otherwise daily.

Oral anticoagulant treatment with a derivative of coumarin was begun on the first or second day and continued for a total of 12 weeks. During treatment with the study drug, prothrombin times were measured at least every other day, with the dose adjusted to achieve an international normalized ratio of 2.0 to 3.0. The study drug was discontinued when the international normalized ratio was maintained above 2.0 for two consecutive days and the patient had received the study drug for at least five days.

Surveillance and Follow-up

All the patients were contacted daily during the initial treatment, after 14 days, and after 12 weeks. At each visit, a checklist was used to elicit information on symptoms and signs of recurrent venous thromboembolism and bleeding. All the patients were instructed to report to the clinical center on an emergency basis if any new symptoms developed that were suggestive of deep-vein thrombosis or pulmonary embolism. In cases of suspected deep-vein thrombosis (for example, when there was increased pain or swelling in the leg) or pulmonary embolism (for example, when there was dyspnea or chest pain), the patients underwent appropriate diagnostic tests. The investigators were asked to report all clinically unusual episodes of bleeding.

During the initial treatment, platelet counts were obtained every third day. Hemoglobin and the hematocrit were measured, and platelet counts obtained, at base line and after 14 days.

Assessment of Clinical Outcomes

The principal outcome events were objectively confirmed symptomatic deep-vein thrombosis or pulmonary embolism and major bleeding within 12 weeks of randomization. Information on all suspected outcome events and deaths was reviewed and classified by a central adjudication committee whose members were unaware of the treatment assignments. A training session was held at the start of the study concerning the techniques and interpretation of the diagnostic tests used.

The criteria for the diagnosis of symptomatic deep-vein thrombosis were as follows: an extension of an intraluminal filling defect on a venogram; a new intraluminal filling defect or an extension of the nonvisualization of proximal veins in the presence of a sudden cutoff defect on a venogram that was seen on at least two projections; if no previous venogram was available for comparison, an intraluminal filling defect; if no venogram was available, abnormal results of compression ultrasonography in an area where compression had been normal or a substantial increase in the diameter of the thrombus during full compression at the popliteal or femoral vein[11,12]; or, if neither a venogram nor an ultrasonographic study was available, a change in the results of impedance plethysmography from normal to abnormal. The criteria for the diagnosis of symptomatic pulmonary embolism were as follows: a new intraluminal filling defect, an extension of an existing defect, or the sudden cutoff of vessels more than 2.5 mm in diameter on a pulmonary angiogram; if no prior angiogram was

available, an intraluminal filling defect or a sudden cutoff of vessels more than 2.5 mm in diameter on a pulmonary angiogram; or if no pulmonary angiogram was available, a defect of at least 75 percent of a segment on the perfusion scan, with normal ventilation. If the ventilation–perfusion scan was nondiagnostic (and no pulmonary angiogram was available), satisfaction of the criteria for deep-vein thrombosis was acceptable; or pulmonary embolism could be demonstrated at autopsy. Only if no adequate objective tests had been performed did the adjudication committee base its final decision on the clinical information provided.

Bleeding was defined as major if it was clinically overt and associated with a fall in the hemoglobin level of at least 2.0 g per deciliter or a need for the transfusion of 2 or more units of red cells; if it was retroperitoneal or intracranial; or if it warranted the permanent discontinuation of treatment. Deaths were classified as due to pulmonary embolism (when there was substantive evidence), sudden death, hemorrhage, or another cause.

Statistical Analysis

On the basis of two recent studies comparing low-molecular-weight heparin with unfractionated heparin, we assumed a 7 percent incidence of recurrent venous thromboembolism with unfractionated heparin and a 20 percent reduction in the relative risk of recurrent venous thromboembolism associated with the use of low-molecular-weight heparin.[11,12] On the basis of the previously observed absolute risk reduction of 12 percentage points associated with the use of unfractionated heparin as compared with placebo,[14] we took an increase of 3 percentage points as the threshold value indicating clinical equivalence. From these assumptions, a study of 1000 patients would provide an 80 percent probability (power) of rejecting, with a one-sided test at a significance level of 0.05, the hypothesis that the rate of recurrence with low-molecular-weight heparin would be more than 3 percentage points higher than that with unfractionated heparin in the entire group of patients with venous thromboembolism.

The rates of recurrent venous thromboembolism were compared by the method of Blackwelder.[15] This statistical test evaluates whether the observed difference excludes the specified threshold for equivalence. For the comparisons of subgroups, the chi-square test (two-sided) was used.

RESULTS

Study Patients

The recruitment of patients began in November 1994 and ended in October 1995. The follow-up of the patients was completed in February 1996. A total of 1745 consecutive patients met the eligibility criteria, among whom 424 (24 percent) met one or more of the criteria for exclusion. The three most common reasons for the exclusion of patients were the use of therapeutic doses of low-molecular-weight heparin, unfractionated heparin, or oral anticoagulant therapy for more than 24 hours (200 patients); contraindications to anticoagulant therapy (68 patients); and difficulty with follow-up because of geographic location (59 patients). Only 12 patients with pulmonary embolism were excluded from the study because thrombolytic therapy was planned. Of the 1321 eligible patients, 1021 (77 percent) gave informed consent and were randomly assigned to low-molecular-weight heparin (510 patients) or unfractionated heparin (511). The base-line characteristics of the patients in the two treatment groups were similar, as Table 1 shows.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.

CHARACTERISTIC	LOW-MOLECULAR-WEIGHT HEPARIN (N=510)	UNFRACTIONATED HEPARIN (N=511)
Demographic variables		
Mean (±SD) age — yr	59.4±17.2	61.6±16.6*
	no. of patients (%)	
Male sex	258 (51)	267 (52)
Medical history		
Previous venous thromboembolism	100 (20)	119 (23)
Surgery within previous 3 mo	164 (32)	130 (25)†
Known cancer	119 (23)	113 (22)
Trauma within previous 3 mo	56 (11)	55 (11)
Bed rest within previous 3 mo	166 (33)	171 (33)
Diagnosis at presentation		
Deep-vein thrombosis only‡	372 (73)	378 (74)
Method of diagnosis		
Compression ultrasonography	288	306
Venography	83	70
Extent of thrombosis		
Calf only	44	58
Proximal	328	320
Pulmonary embolism‡	138 (27)	133 (26)
Method of diagnosis		
Ventilation–perfusion scanning	94	83
Pulmonary angiography§	9	7
Compression ultrasonography§	29	34
Venography§	5	8

*P=0.04 for the comparison between groups.

†P=0.02 for the comparison between groups.

‡In retrospect, three patients with deep-vein thrombosis only and two with pulmonary embolism did not have abnormal test results at entry.

§This diagnostic method was used to detect clinically suspected pulmonary embolism because there was no high-probability ventilation–perfusion scan.

Treatment and Follow-up

Data on the initial treatment, hospitalization, and oral anticoagulation are shown in Table 2. The initial heparin treatment lasted approximately six days in both treatment groups, and the international normalized ratio was in the therapeutic range for similar proportions of time in the two groups. The mean hospital stay was three days less in the group assigned to low-molecular-weight heparin, mainly because 100 of the 372 patients with deep-vein thrombosis assigned to that group (27 percent) were not admitted to the hospital for treatment of their deep-vein thrombosis. Another 56 of the patients with deep-vein thrombosis in that group (15 percent) were discharged during the first three days of treatment. Compliance with treatment and with the study protocol was high, and no patient was lost to follow-up.

Recurrent Venous Thromboembolism

Among the 510 patients treated with low-molecular-weight heparin, 82 patients had a total of 98 episodes of clinically suspected recurrent venous

TABLE 2. DATA ON THE INITIAL HEPARIN TREATMENT, HOSPITALIZATION, AND ORAL ANTICOAGULANT THERAPY.*

VARIABLE	LOW-MOLECULAR-WEIGHT HEPARIN (N=510)	UNFRACTIONATED HEPARIN (N=511)
Initial treatment (days)	6.3±2.4	5.8±2.1
Dose of unfractionated heparin (IU/24 hr)		
Day 1	—	29,610±6623
Day 2	—	28,631±7802
Hospitalization (days)	6.4±7.1	9.4±7.8
INR in therapeutic range at end of initial treatment (% of patients)	87	85
Level of anticoagulation (% of time)		
INR <2.0	22	24
INR 2.0–3.0	57	57
INR >3.0	21	19
Oral anticoagulation for >11 wk (% of patients)	95	94

*Plus–minus values are means ±SD. INR denotes international normalized ratio.

TABLE 3. RATES OF RECURRENT VENOUS THROMBOEMBOLISM, MAJOR BLEEDING, AND DEATH DURING THE STUDY.

VARIABLE	LOW-MOLECULAR-WEIGHT HEPARIN (N=510)	UNFRACTIONATED HEPARIN (N=511)
	no. of patients (%)	
Recurrent venous thromboembolism		
Days 0–14	16	15
Days 15–42	9	7
Days 43–84	2	3
Entire study	27 (5.3)	25 (4.9)
Major bleeding		
Days 0–14	10	8
Days 15–42	1	3
Days 43–84	5	1
Entire study	16 (3.1)	12 (2.3)*
Death		
Days 0–14	5	4
Days 15–42	17	15
Days 43–84	14	20
Entire study	36 (7.1)	39 (7.6)†

*P=0.63 for the comparison between groups.

†P=0.89 for the comparison between groups.

thromboembolism. Of these episodes, 29 (in 27 patients, or 5.3 percent of the total) met the criteria for documented recurrent venous thromboembolism. Among the 511 patients treated with unfractionated heparin, 75 had a total of 88 suspected episodes that were adjudicated, and 30 episodes (in 25 patients, or 4.9 percent) met the criteria. The absolute difference of 0.4 percentage point between these rates indicates equivalence between the treatments, since it rules out an increase of 2.7 percentage points or more with low-molecular-weight heparin as compared with standard heparin at the 95 percent level of confidence (P=0.030 for the comparison with the preset difference of 3 percentage points).

The majority of the recurrent venous thromboembolic events occurred during the first 14 days, and the risk of recurrence decreased over time (Table 3). In 17 of the 27 patients assigned to low-molecular-weight heparin who had recurrences, the event was symptomatic deep-vein thrombosis; in the unfractionated-heparin group, the corresponding number was 13 of 25. In all patients except one, recurrent episodes of venous thromboembolism were documented by objective tests or at autopsy. Adjustment by logistic-regression analysis for differences in age and in the frequency of recent surgery at base line did not alter the results of the study.

Bleeding Complications

Among the reported instances of clinically important bleeding, 93 were confirmed by the central adjudication committee, and 28 of them met the criteria for major bleeding. There were 46 events among the patients treated with low-molecular-weight heparin and 47 among those treated with unfractionated heparin; 16 and 12 of these, respectively, involved major bleeding. As Table 3 shows, the majority of instances of bleeding occurred during the first 14 days of the study.

Mortality

During the 12 weeks of follow-up, 75 patients (7.3 percent) died: 36 who were treated with low-molecular-weight heparin (7.1 percent) and 39 who were treated with unfractionated heparin (7.6 percent). The mortality rate remained fairly constant over time (Table 3). Among the 36 deaths of patients treated with low-molecular-weight heparin, 3 (on days 3, 4, and 35) were classified as due to pulmonary embolism and 3 (on days 18, 55, and 73) were considered sudden. There were no instances of fatal bleeding in this group. Among the 39 deaths in the unfractionated-heparin group, there were 3 fatal episodes of pulmonary embolism (on days 3, 24, and 64), 2 sudden deaths (on days 19 and 44), and 2 instances of fatal bleeding (on days 4 and 5). All six fatal episodes of pulmonary embolism occurred in patients who had pulmonary embolism at presentation.

Additional Observations

Among the 271 patients with pulmonary embolism at presentation, 16 had symptomatic recurrent venous thromboembolism (5.9 percent; 8 patients in each treatment group), as compared with 36 of the 750 patients presenting with deep-vein thrombosis only (4.8 percent; 19 patients treated with

low-molecular-weight heparin and 17 treated with unfractionated heparin). Among the 16 patients presenting with pulmonary embolism who had recurrent thromboembolism, 11 (69 percent) had recurrences of pulmonary embolism, whereas pulmonary embolism occurred in only 11 of the 36 patients with deep-vein thrombosis at presentation (31 percent, $P=0.023$). Among the 232 patients with cancer at base line, 20 (8.6 percent) had symptomatic recurrent venous thromboembolism, as compared with only 32 (4.1 percent) of the remaining 789 patients ($P=0.009$). Forty-seven of the patients with cancer (20.3 percent) died, as compared with 28 (3.5 percent) of those without cancer ($P<0.001$).

The relative effects of low-molecular-weight heparin and unfractionated heparin with respect to the three major clinical outcomes were similar in all these subgroups. They were also similar in other subgroups, such as patients with a history of venous thromboembolism and patients without such a history.

DISCUSSION

Previous randomized trials have shown that subcutaneous, low-molecular-weight heparin is likely to be at least as effective and safe as unfractionated heparin in treating patients with uncomplicated deep-vein thrombosis.[16-18] However, because these trials did not include patients with pulmonary embolism and because some patients with a history of venous thromboembolism were excluded, clinicians may legitimately be concerned that the findings may not translate directly to their own clinical practice.[19]

We studied a broad range of patients, including a large subgroup with pulmonary embolism, in many hospitals in several countries. Unmonitored, subcutaneous low-molecular-weight heparin was shown to be an effective and safe treatment for patients with venous thromboembolism. We observed similar treatment effects in each of various sizable subgroups — patients with pulmonary embolism, cancer, or previous thromboembolism and those without each of these conditions. We also included patients with symptomatic calf-vein thrombosis, who would normally receive anticoagulant therapy, since it has been documented that such patients are at risk for recurrent venous thromboembolism if left untreated.[20] Our predetermined criterion for equivalence between the treatments was an absolute increase in the recurrence rate of no more than 3 percentage points with low-molecular-weight heparin. Since our findings showed that there was no such difference, one may conclude that the treatments are equivalent for patients with venous thromboembolism. It should be understood that the study did not have the power to detect differences among subgroups of patients.

Thus, in terms of safety and efficacy, low-molecular-weight heparin offers an appropriate alternative to unfractionated heparin in patients with venous thromboembolism. In addition, low-molecular-weight heparin has several practical advantages. Since there is no need for laboratory monitoring or infusion, suitable patients can be treated at home, either throughout their care or after early discharge from the hospital.[11,12] Those requiring hospital admission also benefit because they avoid the inconvenience and hazards of intravenous lines.

Because this was an open trial, care was taken to minimize the potential for bias. We included consecutive patients, used central randomization by telephone, and ensured that follow-up was complete for all randomized patients. Furthermore, all clinically suspected outcome events were assessed by an independent, blinded central adjudication committee on the basis of predetermined criteria.

Meta-analyses of early trials of low-molecular-weight heparins for the treatment of deep-vein thrombosis have suggested that, as compared with unfractionated heparin, these agents may be associated with reductions as large as 50 percent in the relative risk of recurrent thrombosis.[16-18] Our findings are inconsistent with a reduction of this magnitude. Explanations for the apparent discrepancy, other than that it occurred by chance, include the possibility that low-molecular-weight heparins are associated with a more modest reduction, if any. This possibility is supported by two recent studies.[11,12] It is noteworthy that the rates of recurrent venous thromboembolism with low-molecular-weight heparins in the various treatment trials are consistent, around 4 to 5 percent, whereas the rates among the groups treated with unfractionated heparin vary more widely; the latter variation may be due in part to differences in the regimens of unfractionated heparin in the different trials.[9-12,21-24] The incidence of major bleeding reported for both groups in this study is consistent with that reported previously.[16-18]

Overall, the rates of recurrence we observed were low, whether patients were treated with low-molecular-weight heparin or with unfractionated heparin. In patients with cancer, however, the recurrence rate was doubled in both treatment groups, suggesting that anticoagulant therapy in these patients needs further improvement.

We conclude that low-molecular-weight heparin and unfractionated heparin are equally effective and safe in unselected patients with confirmed deep-vein thrombosis, with or without associated pulmonary embolism. In addition, low-molecular-weight heparin permits treatment regimens to be simplified so that hospital stays can be shortened and suitable patients can be treated outside the hospital.

Supported by a grant from Knoll AG, Ludwigshafen, Germany.

APPENDIX

In addition to the members of the Writing Committee, the following institutions and investigators participated in the study. **Executive Committee:** J.W. ten Cate, H.R. Büller, M. Gent, J. Hirsh, M.H. Prins, and R. Baildon; **Adjudication Committee:** A.W.A. Lensing, D.R. Anderson, and E.J.R. van Beek; **Safety Committee:** J.N. Fiesinger and J.G.P. Tijssen; **Coordination and Data Management Centers:** *Academic Medical Center, University of Amsterdam, Amsterdam* — A. van Barneveld, L.T. Eimers, Y.P. Graafsma, R. Hettiarachchi, B. Hutten, and K. Redekop; *Hamilton Civic Hospitals Research Center, Hamilton, Ont., Canada* — S. Haley, L. Liberale, T. Finch, S. Whittaker, and L. Wilkinson; **Participating Centers** (the number of patients contributed by the center follows the name of the center): *Institute of Medical Semiotics, Padua, Italy* (96) — P. Prandoni, S. Villalta, B. Girolami, P. Bagatella, L. Rossi, and A. Girolami; *Medicina Interna e Oncologia Medica, Policlinico "San Matteo," Pavia, Italy* (81) — F. Piovella, M. Barone, C. Beltrametti, S. Serafini, S. Siragusa, and E. Ascari; *Victoria Hospital and University of Western Ontario, London, Ont., Canada* (75) — M.J. Kovacs, B. Morrow, and J. Kovacs; *Academic Medical Center, University of Amsterdam, Amsterdam* (71) — P.M.M. Kuijer, M.M.W. Koopman, and H. Jagt; *Hamilton Civic Hospitals, Henderson General Division, Hamilton, Ont., Canada* (53) — J. Weitz, C. Kearon, and L. Biagioni; *Krankenhaus Bogenhaussen–Medizinische Poliklinik, Munich, Germany* (52) — S. Haas, F. Lössner, F.A. Spengel, and M. Berger; *Hôpital du Saint-Sacrement, Quebec, Que., Canada* (51) — C. Demers and J. Poulin; *University Hospital Groningen, Groningen, the Netherlands* (41) — J. van der Meer, G.T.H. Que, and W.M. Smid; *Victoria General Hospital, Halifax, N.S., Canada* (38) — D.R. Anderson, K.S. Robinson, and E. Boyle; *Montreal General Hospital, Montreal* (35) — J.R. Leclerc, B. St. Jacques, and S. Finkenbine; *Flinders Medical Centre, Adelaide, Australia* (33) — A.S. Gallus, D. Cohlan, and C. Rich; *Slotervaart Hospital, Amsterdam* (33) — D.P.M. Brandjes, C.A. Hoefnagel, M. de Rijk, and F. Turkstra; *Centre Hospitalier de l'Université Laval, Quebec, Que., Canada* (30) — L. Desjardins, J. Cote-Desjardins, L. Couture, M. Ruel, and J. Villeneuve; *Sunnybrook Health Science Centre, Toronto* (29) — W.H. Geerts, R.M. Jay, and K.I. Code; *Hamilton Civic Hospitals, Hamilton General Division, Hamilton, Ont., Canada* (29) — A.G.G. Turpie and J. Johnson; *Hôtel Dieu, Montreal* (28) — P. Nguyen, J.R. Cusson, and S. Roy; *Ottawa Civic Hospital, Ottawa, Ont., Canada* (28) — P.S. Wells, J. Bormanis, and D. Goudie; *University Hospital, London, Ont., Canada* (26) — M. Cruickshank and M. von Lewinski; *Hospital Germans Trias i Pujol, Barcelona, Spain* (24) — M. Monreal, J.C. Sahuquillo, and E. Lafoz; *Hôpital Antoine Béclère, Clamart, France* (20) — G. Simonneau, F. Parent, and J. Jagot; *St. Joseph's Hospital, Hamilton, Ont., Canada* (19) — J.D. Douketis and K. Kinnon; *McMaster University Medical Centre, Hamilton, Ont., Canada* (19) — J.S. Ginsberg, P. Brill-Edwards, and D. Donovan; *Auckland Hospital, Auckland, New Zealand* (18) — P.A. Ockelford; *Hôpital Maisonneuve-Rosemount, Montreal* (18) — J. Kassis and S. Bornais; *Centre Hospitalier Universitaire Hôtel Dieu, Nantes, France* (17) — B. Planchon, D. El Kouri, and M.A. Pistorius; *Hospital de 12 Octubre, Madrid* (13) — M. Escribano and G. Garrido; *Prince of Wales Hospital, Sydney, Australia* (13) — C.N. Chesterman, B.H. Chong, and S. Pritchard; *Royal Melbourne Hospital, Melbourne, Australia* (10) — J.F. Cade, T. Bynon, and J. Stanford; *St. Joseph's Health Centre, London, Ont., Canada* (9) — W.M. Brien and B. Palmer; *Clinique Saint Vincent, Besançon, France* (9) — R. Faivre and P.Y. Petiteau; *Hemophilia and Thrombosis Center A. Bianchi Bonomi, Maggiore Hospital, Milan, Italy* (5) — P.M. Manucci, M. Moia, and P. Bucciarelli.

REFERENCES

1. Kierkegaard A. Incidence of acute deep vein thrombosis in two districts: a phlebographic study. Acta Chir Scand 1980;146:267-9.

2. Nordström M, Lindblad B, Bergqvist D, Kjellström T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med 1992;232:155-60.

3. van Beek EJR, Büller HR, ten Cate JW. Epidemiology of venous thromboembolism. In: Tooke JE, Lowe GD, eds. A textbook of vascular medicine. London: Arnold, 1996:471-88.

4. Huisman MV, Büller HR, ten Cate JW, et al. Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. Chest 1989;95:498-502.

5. Hull RD, Hirsh J, Carter CJ, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. Ann Intern Med 1983;98:891-9.

6. Kruit WHJ, de Boer AC, Sing AK, van Roon F. The significance of venography in the management of patients with clinically suspected pulmonary embolism. J Intern Med 1991;230:333-9.

7. Clark S. Current issues in management of thrombosis. Lancet 1995; 346:113-4.

8. Hirsh J. Heparin. N Engl J Med 1991;324:1565-74.

9. Prandoni P, Lensing AWA, Büller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet 1992;339:441-5.

10. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992;326:975-82.

11. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996;334:677-81.

12. Koopman MMW, Prandoni P, Piovella F, 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. N Engl J Med 1996;334:682-7.

13. Cruickshank MK, Levine MN, Hirsh J, Roberts R, Siguenza M. A standard heparin nomogram for the management of heparin therapy. Arch Intern Med 1991;151:333-7.

14. Brandjes DPM, Heijboer H, Büller HR, de Rijk M, Jagt H, ten Cate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. N Engl J Med 1992;327: 1485-9.

15. Blackwelder WC. "Proving the null hypothesis" in clinical trials. Control Clin Trials 1982;3:345-53.

16. Lensing AWA, Prins MH, Davidson BL, Hirsh J. Treatment of deep venous thrombosis with low-molecular-weight heparins: a meta-analysis. Arch Intern Med 1995;155:601-7.

17. Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. Am J Med 1996;100:269-77.

18. 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. BMJ 1994;309:299-304.

19. Schafer AI. Low-molecular-weight heparin — an opportunity for home treatment of venous thrombosis. N Engl J Med 1996;334:724-5.

20. Lagerstedt CI, Olsson CG, Fagher BO, Oqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet 1985;2:515-8.

21. Lopaciuk S, Meissner AJ, Filipecki S, et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. Thromb Haemost 1992;68:14-8.

22. Simonneau G, Charbonnier B, Decousus H, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Arch Intern Med 1993;153:1541-6.

23. Lindmarker P, Holmström M, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. Thromb Haemost 1994;72:186-90.

24. Albada J, Nieuwenhuis HK, Sixma JJ. Treatment of acute venous thromboembolism with low molecular weight heparin (Fragmin): results of a double-blind randomized study. Circulation 1989;80:935-40.