Low-molecular weight heparin in the treatment of patients with venous thromboembolism: the Columbus Investigators
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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.)
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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 Zuidoost, 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 more than 60 kg; 4200 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.7 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 vein11,12; 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. 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,

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 was 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. 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 thrombotic 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.

#### 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

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### 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
thrombosis only (4.8 percent; 19 patients treated with unfractionated 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.

**Table 3. Rates of Recurrent Venous Thromboembolism, Major Bleeding, and Death during the Study.**

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

*P = 0.63 for the comparison between groups.
†P = 0.89 for the comparison between groups.

Thrombosis only (4.8 percent; 19 patients treated with unfractionated 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 FOR PATIENTS WITH VENOUS THROMBOEMBOLISM

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. 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. 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. 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. 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. 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. 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. The incidence of major bleeding reported for both groups in this study is consistent with that reported previously.

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.

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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. Buil., M. Gent, J. Hirsh, M.H. Prins, and R. Baildon; Adjudication Committee: A.W.A. Lensing, D.R. Anderson, and E.J.R. van Beck; 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, T.J. Eimers, Y.P. Graabm, R. Hettiarachchi, B. Hutten, and K. Redekop; Hamilton Civic Hospitals Research Center, Hamilton, Ont., Canada — S. Haley, L. Liberal, 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, Pedia, Italy (96) — P. Prandoni, S. Vidalta, 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. Scarrati, 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. Kuiper, M.M.W. Koopman, and H. Jago; Hamilton Civic Hospitals, Henderson General Division, Hamilton, Ont., Canada (53) — J. Weitz, C. Kearon, and L. Brigioni; Krankenhaus Bogenhausen—Medizinische Poliklinik, Munich, Germany (52) — S. Haas, F. Loosner, A. Spengel, and M. Berger; Hôpital du Sacré-Coeur, 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. Smit; Victoria General Hospital, Halifax, N.S., Canada (38) — D.R. Anderson, K.S. Robinson, and E. Boyle; Montreal General Hospital, Montreal (35) — J.R. Leckner, B. St. Jacques, and S. Finkenbine; Flanders Medical Centre, Adelaide, Australia (35) — A.S. Gallus, D. Cohlan, and C. Rich; Sloterwaard Hospital, Amsterdam, the Netherlands (33) — A.W.A. Lensing, D.R. Anderson, and 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. Cuison, and S. Roux; Ottawa Civic Hospital, Ottawa, Ont., Canada (28) — P.S. Wells, J. Bornanis, and D. Goudie; University Hospital, London, Ont., Canada (26) — M. Cruickshank and M. van Lewinski; Hospital Germans Trias i Pujol, Barcelona, Spain (24) — M. Monreal, J.C. Sahuaquillo, and E. Lafoz; Hôpital Ambroise Béclère, Clamart, France (20) — G. Simonneau, F. Parent, and J. Jastog; 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. Bril-Edwards, and D. Donovan; Auckland Hospital, Auckland, New Zealand (18) — P.A. Ockelford; Hôpital Massoneuve-Raouinoot, Montréal (18) — J. Kasas and S. Bornas; Centre Hospitalier Universitaire Hôtel-Dieu, Nanterre, 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. Chung, 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, Beaune, France (9) — R. Paire and P.Y. Petitjean; Hemothilia and Thrombus Centre A. Bianchi Bonomi, Maggiore Hospital, Milan, Italy (5) — P.M. Manucci, M. Mosa, and P. Bucciarelli.

REFERENCES