Low-Molecular-Weight Heparin Compared with Intravenous Unfractionated Heparin for Treatment of Pulmonary Embolism

A Meta-Analysis of Randomized, Controlled Trials

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Background: **Low-molecular-weight heparin has greatly simplified the management of deep venous thrombosis. However, for patients who present with pulmonary embolism, the role of low-molecular-weight heparin is uncertain and unfractionated heparin remains widely used.**

Purpose: **To compare the efficacy and safety of fixed-dose subcutaneous low-molecular-weight heparin with that of dose-adjusted intravenous unfractionated heparin to treat acute pulmonary embolism.**

Data Sources: **The MEDLINE, EMBASE, and Cochrane Library databases were searched up to 1 August 2003. Additional data sources were manual searches of abstract proceedings and personal contact with investigators and pharmaceutical companies.**

Study Selection: **Randomized trials comparing fixed-dose subcutaneous low-molecular-weight heparin with dose-adjusted intravenous unfractionated heparin for the treatment of nonmassive symptomatic pulmonary embolism or asymptomatic pulmonary embolism in the context of symptomatic deep venous thrombosis.**

Data Extraction: **Two reviewers independently selected studies and extracted data on study design; quality; and clinical outcomes, including symptomatic venous thromboembolism, death, and major and minor bleeding. Odds ratios for individual outcomes were calculated for each trial and were pooled by using the Mantel–Haenszel method.**

Data Synthesis: **Fourteen trials involving 2110 patients with pulmonary embolism met the inclusion criteria. Separate outcome data for patients with pulmonary embolism were not available from 2 trials (159 patients), leaving 12 trials for meta-analysis. Compared with unfractionated heparin, low-molecular-weight heparin was associated with a non–statistically significant decrease in recurrent symptomatic venous thromboembolism at the end of treatment (1.4% vs. 2.4%; odds ratio, 0.63 [95% CI, 0.33 to 1.18]) and at 3 months (3.0% vs. 4.4%; odds ratio, 0.68 [CI, 0.42 to 1.09]). Similar estimates were obtained for patients who presented with symptomatic pulmonary embolism (1.7% vs. 2.3%; odds ratio, 0.72 [CI, 0.35 to 1.48]) or asymptomatic pulmonary embolism (1.2% vs. 3.2%; odds ratio, 0.53 [CI, 0.15 to 1.88]). For major bleeding complications, the odds ratio favoring low-molecular-weight heparin (1.3% vs. 2.1%; odds ratio, 0.67 [CI, 0.36 to 1.27]) was also not statistically significant.**

Conclusions: **Fixed-dose low-molecular-weight heparin treatment appears to be as effective and safe as dose-adjusted intravenous unfractionated heparin for the initial treatment of nonmassive pulmonary embolism.**

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Low-molecular-weight heparin has greatly simplified the initial management of deep venous thrombosis because it is at least as effective and safe as unfractionated heparin and can be administered subcutaneously at fixed doses without laboratory monitoring (1). These features allow a substantial proportion of patients with deep venous thrombosis to be treated at home without being admitted, improving their quality of life and reducing health care costs (2, 3).

The role of fixed-dose low-molecular-weight heparin as therapy for patients with acute pulmonary embolism is less certain. Many clinicians continue to treat pulmonary embolism with dose-adjusted intravenous unfractionated heparin because of concern that patients with pulmonary embolism are at higher risk for fatal outcomes than are those who present with deep venous thrombosis alone, and because evidence that low-molecular-weight heparin is effective and safe for the treatment of pulmonary embolism is believed to be insufficient (4). However, deep venous thrombosis and pulmonary embolism share a common pathophysiologic process and risk factors, and postmortem studies indicate that the majority of patients with pulmonary embolism also have thrombosis involving the leg veins (5). Moreover, several randomized trials have suggested that patients with symptomatic pulmonary embolism (6, 7) or asymptomatic pulmonary embolism in the context of symptomatic deep venous thrombosis (8, 9) can be treated with low-molecular-weight heparin instead of unfractionated heparin. Consequently, pulmonary embolism and deep venous thrombosis are now increasingly recognized as different manifestations of the same disease process, collectively known as *venous thromboembolism,* and may also reasonably be expected to respond similarly to treatment with low-molecular-weight heparin.

To further clarify the efficacy and safety of low-molecular-weight heparin for the initial treatment of pulmonary embolism, we performed a meta-analysis of all randomized trials that compared fixed-dose low-molecular-weight heparin with dose-adjusted intravenous unfractionated heparin for this indication. We included trials that enrolled patients with symptomatic pulmonary embolism or asymptomatic pulmonary embolism in the context of symptomatic deep venous thrombosis. The primary outcome was recurrent symptomatic venous thromboembolism, including deep venous thrombosis and pulmonary embolism, at the end of treatment. Secondary outcomes were recurrent

Context

Several trials have compared benefits and harms of fixed-dose subcutaneous low-molecular-weight heparin with dose-adjusted intravenous unfractionated heparin in patients with pulmonary embolus.

Contribution

This meta-analysis of 12 randomized trials compared the 2 heparin-based therapies and found nonstatistically significant reductions in risks for recurrent thromboembolism and major bleeding with low-molecular-weight heparin.

Implications

Low-molecular-weight heparin may be a safe and efficacious alternative to unfractionated heparin for some patients with pulmonary embolus.

Cautions

Small numbers of events in the trials limited the authors' ability to precisely determine whether the 2 therapies had similar or different effects.

–The Editors

symptomatic venous thromboembolism at 3 months, all-cause mortality, and major and minor bleeding.

METHODS

A protocol was prospectively developed in which the specific objectives, criteria for study selection, the approach to assessing study quality, primary and secondary outcomes, and statistical methods were defined.

Study Identification

We attempted to identify all relevant published and unpublished unconfounded randomized trials that compared fixed-dose low-molecular-weight heparin with dose-adjusted intravenous unfractionated heparin for the initial treatment of pulmonary embolism. We searched electronic databases (MEDLINE and EMBASE) and the Cochrane Library to 1 August 2003 by using the terms *thrombosis*, *thromboembolism*, *pulmonary embolism*, *randomized controlled trial*, *controlled clinical trial*, and *random*, in combination with generic and trade names of individual preparations of low-molecular-weight heparin. We manually searched the bibliographies of journal articles to locate additional studies, reviewed abstracts from major international meetings, and contacted manufacturers of low-molecular-weight heparin agents to learn of unpublished studies. Relevance was assessed by using a hierarchical approach based on title, abstract, and published or unpublished articles.

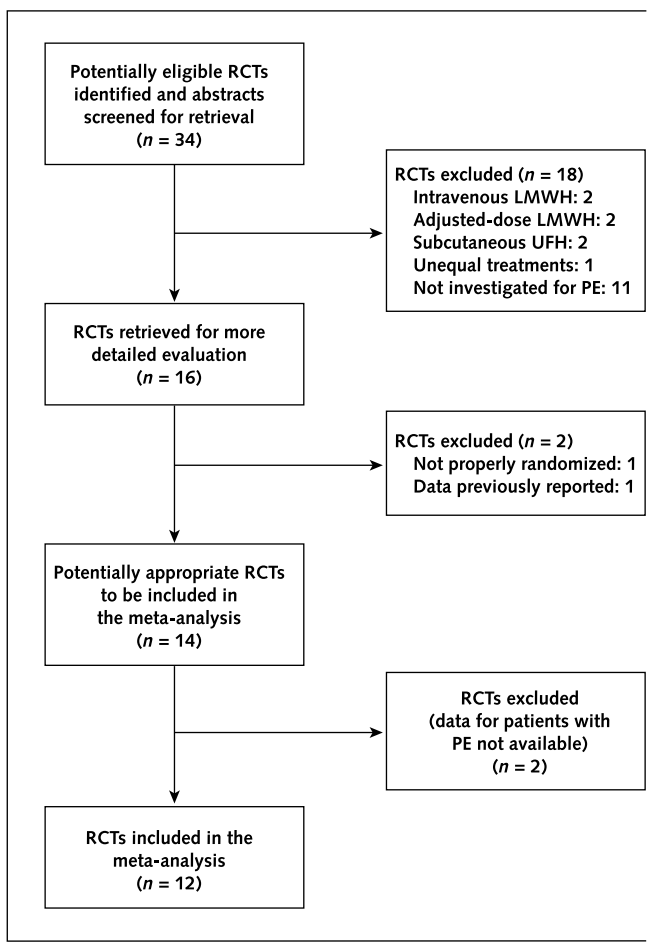
Study Selection

Two investigators independently evaluated studies for possible inclusion, and disagreements were resolved by discussion. To be included, studies had to be properly randomized; include patients with objectively diagnosed symptomatic pulmonary embolism or objectively diagnosed asymptomatic pulmonary embolism in addition to symptomatic deep venous thrombosis; compare fixed-dose low-molecular-weight heparin with dose-adjusted intravenous unfractionated heparin; and use objective methods to assess one or more clinical outcomes, including recurrent symptomatic venous thromboembolism, major bleeding, minor bleeding, and death. The type of low-molecular-weight heparin preparation, dose, duration of treatment, or duration of follow-up was not used to determine eligibility of studies for inclusion.

Assessment of Study Quality

We used the study-quality criteria of Schultz and colleagues (10) to evaluate the studies included in our meta-analysis. These criteria include proper generation of the treatment allocation sequence, proper concealment of the allocation sequence, blinding of the patient and the investigator who assessed clinical outcomes to treatment allocation, and completeness of follow-up.

Figure 1. **Process of study selection.**



LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RCT = randomized, controlled trial; UFH = unfractionated heparin.

Table 1. **Design of Trials Included in the Meta-Analysis***

Author, Year (Reference)	Eligibility Criteria	Patients†	Mean Age	Women	Dosage of Low-Molecular-Weight Heparin	Dosage of Unfractioned Heparin	Duration of Therapy	Duration of Follow-up
		n	*y*	%			*d*	
European multicentre study, 1991 (36)	Symptomatic proximal DVT‡	108	62	43	Nadroparin, 4750–6650 antifactor Xa IU twice daily§	No bolus Infusion, 20 IU/kg per hour	10	3 mo
Hull et al., 1992 (8, 32)	Symptomatic proximal DVT	200	64% age ≥ 60 y	56	Tinzaparin, 175 IU/kg once daily	Bolus, 5000 IU Infusion, 29 760–40 320 IU/d	6	3 mo
Prandoni et al., 1992 (37)	Symptomatic proximal DVT; no suspicion of PE	91	51% age > 65 y	39	Nadroparin, 4750–6650 antifactor Xa IU twice daily§	Bolus, 100 IU/kg Infusion, 35 000 IU/d	10	6 mo
Thery et al., 1992 (38)	Symptomatic PE	68‖	62	57	Nadroparin, 76 IU/kg twice daily	Bolus 50 IU/kg Infusion 600 IU/kg per day	14	14 d
Kuijer et al., 1995 (13)	Symptomatic PE	67¶	60	49	Dalteparin, 120 IU/kg twice daily	Bolus, 5000 IU Infusion, 1250 IU/h	5	3 mo
Meyer et al., 1995 (39)	Symptomatic PE	60**	61	57	Dalteparin, 120 IU/kg twice daily	No bolus Infusion, 500 IU/kg per day	10	3 mo
Columbus Trial 1997 (6)	Symptomatic VTE	271	66	56	Reviparin, 3500–6300 IU twice daily§	Bolus, 5000 IU Infusion, 1250 IU/h	5	3 mo
Simonneau et al., 1997 (7)	Symptomatic PE	608††	56	65	Tinzaparin, 175 IU/kg once daily	Bolus, 50 IU/kg Infusion, 500 IU/kg per day	5	3 mo
Campbell et al., 1998 (40)	Symptomatic PE	16	72	52	Tinzaparin, 175 IU/kg once daily	Bolus, 5000 IU Infusion, 1400 IU/h	5	3 mo‡‡
Decousus et al., 1998 (41)	Symptomatic proximal DVT ± PE or increased risk of PE§§	95	58	46	Enoxaparin, 1 mg/kg twice daily	Bolus, 5000 IU Infusion, 500 IU/kg per day	8–12	2 y
Kirchmaier et al., 1998 (42)	Symptomatic DVT ± PE	80‖‖	62	40	Certoparin, 8000 IU twice daily	Bolus, 5000 IU Infusion, 20 IU/kg per hour	14	6 mo
Merli et al., 2001 (9)	Symptomatic DVT ± PE	287	61	45	Enoxaparin, 1 mg/kg twice daily or 1.5 mg/kg once daily	Heparin nomogram at local institution	5	3 mo

* DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
† Patients with symptomatic PE or asymptomatic abnormalities on ventilation–perfusion scanning at study entry.
‡ Asymptomatic PE was diagnosed by perfusion scanning and was defined as pulmonary vascular obstruction of at least 5%.
§ Adjusted for body weight.
‖ Dose-ranging study; only patients with PE receiving what is now accepted as a therapeutic dose of low-molecular-weight heparin are included here.
¶ 20 additional patients with suspected symptomatic PE were randomly allocated but subsequently not confirmed to have PE. Outcome data for an additional 2 patients were not available.
** 88 patients were randomly allocated; the diagnosis of PE was not confirmed in 14 patients, and outcome data for an additional 14 patients randomly assigned in Austria are not available.
†† Intention-to-treat data on outcomes were not available for 4 patients.
‡‡ Range, 1 to 5 months.
§§ Does not include patients who were also randomly allocated to insertion of a caval filter.
‖‖ Does not include patients treated with intravenous low-molecular-weight heparin.

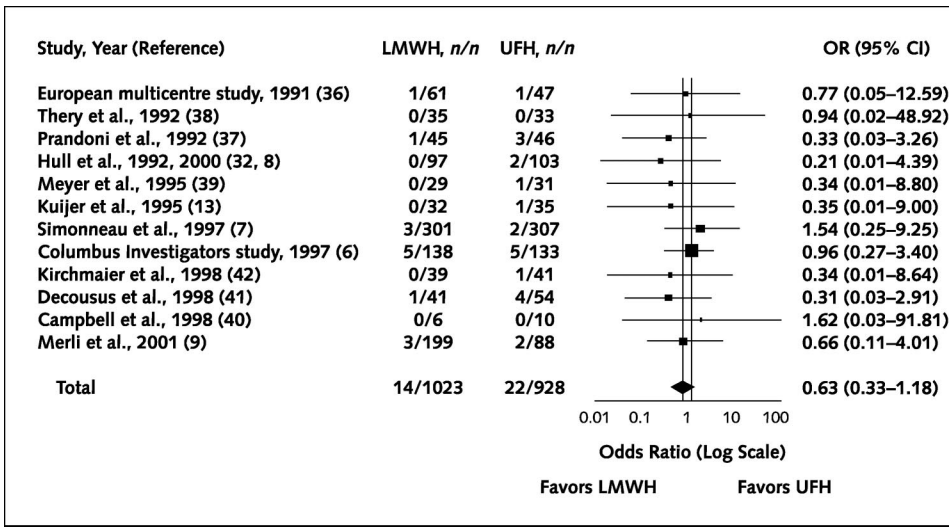
Data Extraction

Two investigators independently extracted data on study design, study quality, and the following efficacy and safety outcomes at the end of treatment and at 3 months: symptomatic venous thromboembolism, death, major bleeding, and minor bleeding. We accepted the investigators' definitions of deep venous thrombosis, pulmonary embolism, and major and minor bleeding. The data abstracted for each trial were confirmed by reviewer consensus and were sent to the first or corresponding author for verification. Missing data were requested from the investigators or sponsoring company at that time.

Statistical Analysis

We used a fixed-effects model based on the Mantel–Haenszel method for combining results from the individual trials (11). This model is also known as an *assumption-free model* because it does not assume that included studies

Figure 2. **Symptomatic venous thromboembolism at the end of treatment in trials comparing low-molecular-weight heparin (*LMWH*) with unfractionated heparin (*UFH*) for the treatment of acute pulmonary embolism.**



Data for the study by Hull and colleagues (32) are estimated from the published time-to-event curve. OR = odds ratio.

are a random sample of the universe of studies and it provides a pooled estimate of treatment effect that is conditional on the available trial data. We calculated the odds ratio and 95% CIs. The test of heterogeneity was calculated by using the Mantel–Haenszel method. All statistical calculations were performed by using Comprehensive Meta Analysis software, version 1.0.23 (Biostat, Englewood, New Jersey).

We performed sensitivity analyses to further establish the robustness of our results. To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we deleted studies one at a time. We examined the effect of excluding lower-quality studies (open-label studies and those with incomplete follow up) from the analysis. An inverted funnel plot of treatment effect versus study precision was created for the primary outcome to detect publication bias (12), a technique that may be helpful to determine whether additional small studies may have been conducted but not published because of unfavorable or negative results. Finally, results obtained by using a fixed-effects model were compared with those obtained by using a random-effects model.

RESULTS

Study Selection

Figure 1 shows the process of study selection. We identified 551 potentially eligible citations. We excluded 517 citations after scanning their titles and abstracts, leaving 34 citations for further evaluation. We obtained the completed but unpublished manuscript for one abstract (13) from the authors. We excluded 18 studies in which low-molecular-weight heparin was administered intravenously (14, 15), the dose of low-molecular-weight heparin was adjusted according to the results of laboratory monitoring (16, 17), unfractionated heparin was administered subcutaneously (18, 19), the duration of treatment with 2 therapies was unequal (20), or patients presenting with deep venous thrombosis were included but objective diagnostic testing was not done to screen for associated asymptomatic pulmonary embolism (21–31). Of the 16 remaining studies, one reported outcome data on the subgroup of patients with pulmonary embolism (8) from a study that had previously been published (32). Contact with the authors of another study revealed that study treatment was allocated by using alternate odd and even numbers (33). These 2 studies were excluded. Two additional studies were excluded because we could not obtain separate outcome data for patients with pulmonary embolism despite contact with the investigators and sponsoring pharmaceutical companies (34, 35). Thus, 12 studies were available for inclusion (6, 9, 13, 32, 34, 36–42).

Study Design

Table 1 shows the designs of the studies. The majority of trials were small, and only 4 trials included 200 or more patients (6–9, 32). Six studies included patients with symptomatic pulmonary embolism (6, 7, 13, 38–40), and 2 included only patients with symptomatic deep venous thrombosis but screened all patients for associated asymptomatic pulmonary embolism at baseline (36, 37). Four studies included patients with symptomatic deep venous thrombosis or pulmonary embolism (9, 32, 41, 42). No trial stratified randomization by the presence or absence of asymptomatic pulmonary embolism at baseline or included patients with massive pulmonary embolism. Six low-molecular-weight heparin preparations were evaluated (certoparin, dalteparin, enoxaparin, nadroparin, reviparin, and tinzaparin). Treatment with low-molecular-weight heparin or unfractionated heparin was continued for a mean of 5 to

14 days, and clinical follow-up was at least 3 months in 11 of the 12 studies.

Study Quality

Proper methods were used to generate the randomized treatment allocation, and treatment allocation appeared to be adequately concealed in all studies (**Appendix Table**, available at www.annals.org). Both patients and investigators were blinded to treatment allocation in only one of the 12 studies. There was 100% clinical follow-up in 5 studies and 90% or greater follow-up in 7 studies.

Symptomatic Venous Thromboembolism at the End of Heparin Treatment

Figure 2 shows data on symptomatic venous thromboembolism at the end of heparin treatment, and **Table 2** shows summary data for the individual components of this outcome. The 3 largest trials accounted for more than half the data for the primary outcome (6, 7, 9). Ten of the 12 studies for which these data were available suggested a decrease in symptomatic venous thromboembolism with low-molecular-weight heparin compared with unfractionated heparin. The pooled estimate from all the trials revealed a statistically nonsignificant decrease in symptomatic events with low-molecular-weight heparin compared with unfractionated heparin (1.4% vs. 2.4%; odds ratio, 0.63 [95% CI, 0.33 to 1.18), with no statistical evidence of heterogeneity among the studies (chi-square = 3.24). A similar estimate of treatment effect was obtained for patients who presented with symptomatic pulmonary embolism (1.7% vs. 2.3%; odds ratio, 0.72 [CI, 0.35 to 1.48]) and for patients who presented with asymptomatic pulmonary embolism in the context of symptomatic deep venous thrombosis (1.2% vs. 3.2%; odds ratio, 0.53 [CI, 0.15 to 1.88]).

Symptomatic Venous Thromboembolism at 3 Months

Table 3 shows summary data on symptomatic venous thromboembolism at 3 months. These data were available from 11 studies; one study did not follow patients for more than 14 days (38). Nine of the 11 studies demonstrated a reduction in symptomatic venous thromboembolism with low-molecular-weight heparin compared with unfractionated heparin. The pooled estimate revealed a statistically nonsignificant decrease in symptomatic events with low-molecular-weight heparin compared with unfractionated heparin (3.0% vs. 4.4%; odds ratio, 0.68 [CI, 0.42 to 1.09]), with no statistical evidence of heterogeneity among the studies (chi-square = 5.93). A similar estimate of treatment effect was obtained for patients who presented with symptomatic pulmonary embolism (3.3% vs. 4.3%; odds ratio, 0.72 [CI, 0.40 to 1.28]) and those who presented with asymptomatic pulmonary embolism in the context of symptomatic deep venous thrombosis (3.5% vs. 3.8%; odds ratio, 1.07 [CI, 0.40 to 2.91]).

All-Cause Mortality

Tables 2 and **3** show data on all-cause mortality at the end of treatment (25 deaths) and at 3 months (101 deaths). The rate of all-cause mortality did not significantly differ between patients who received low-molecular-weight heparin and those who received unfractionated heparin at the end of treatment (1.4% vs. 1.2%; odds ratio, 1.20 [CI, 0.59 to 2.45]) or at 3 months (4.7% vs. 6.1%; odds ratio, 0.77 [CI, 0.52 to 1.15]). No data on cause-specific mortality were available.

Bleeding

Table 4 shows data on bleeding. The incidence of major bleeding was 1.4% among the 1023 patients who received low-molecular-weight heparin compared with 2.3% among the 928 patients who received unfractionated heparin (odds ratio, 0.67 [CI, 0.36 to 1.27]), with no statistical evidence of heterogeneity (chi-square = 5.03). There was a modest but nonsignificant excess of minor bleeding with low-molecular-weight heparin (6.8% vs. 5.5%; odds ratio, 1.08 [CI, 0.73 to 1.59]), with no heterogeneity among the studies (chi-square = 12.78).

Different Low-Molecular-Weight Heparin Preparations

There was no evidence that any low-molecular-weight heparin preparation was better or worse than another in terms of efficacy or safety outcomes (data not shown).

Sensitivity Analyses

Removing individual studies did not materially alter our primary outcome. Likewise, when we removed trials in which patient follow-up was incomplete, our results were

Table 2. **Recurrent Symptomatic Venous Thromboembolism and Death at the End of Treatment**

Outcome	Low-Molecular-Weight Heparin Recipients	Unfractionated Heparin Recipients	Odds Ratio (95% CI)
	n/n (%)		
Any venous thromboembolism	14/1023 (1.4)	22/928 (2.4)	0.63 (0.33–1.18)*
Deep venous thrombosis	1/926 (0.1)†	7/825 (0.8)†	0.47 (0.17–1.26)‡
Pulmonary embolism	13/926 (1.4)†	14/825 (1.7)†	0.91 (0.45–1.85)§
All-cause mortality	14/1023 (1.4)	11/928 (1.2)	1.20 (0.59–2.45)‖

* Heterogeneity: chi-square = 3.24.
† Data on these outcomes were not available from the study by Hull et al. (8, 32).
‡ Heterogeneity: chi-square = 2.32.
§ Heterogeneity: chi-square = 2.61.
‖ Heterogeneity: chi-square = 1.40.

Table 3. **Recurrent Symptomatic Venous Thromboembolism and Death at 3 Months**

Outcome	Low-Molecular-Weight Heparin Recipients	Unfractionated Heparin Recipients	Odds Ratio (95% CI)
	n/n (%)		
Any venous thromboembolism	30/988 (3.0)	39/895 (4.4)	0.68 (0.42–1.09)*
Deep venous thrombosis	15/891 (1.7)†	19/792 (2.4)†	0.64 (0.33–1.25)‡
Pulmonary embolism	16/891 (1.8)†	20/792 (2.5)†	0.78 (0.41–1.47)§
All-cause mortality	46/988 (4.7)	55/895 (6.1)	0.77 (0.52–1.15)‖

* Heterogeneity: chi-square = 5.93.
† Data for these outcomes were not available from the study by Hull et al. (8, 32).
‡ Heterogeneity: chi-square = 2.83.
§ Heterogeneity: chi-square = 2.51.
‖ Heterogeneity: chi-square = 4.40.

unchanged. A funnel plot of effect size versus study precision was relatively symmetrical, with a similar number of studies on either side of the summary treatment effect for symptomatic venous thromboembolism at the end of treatment (data not shown). This finding is consistent with a lack of major publication bias. No important differences were seen between results obtained by using the fixed-effects model versus the random-effects model.

DISCUSSION

Our results suggest that in terms of thromboembolic recurrences and major bleeding complications, low-molecular-weight heparin is as effective and safe as unfractionated heparin for the initial treatment of pulmonary embolism. A similar estimate of treatment effect for all outcomes was found in patients with symptomatic compared with asymptomatic pulmonary embolism. Estimates of treatment effect were unchanged after removal of individual studies or those with incomplete follow-up and regardless of which statistical approach was used, emphasizing the robustness of our results. Nonetheless, our conclusions concerning the relative efficacy and safety of low-molecular-weight heparin and unfractionated heparin for the initial treatment of pulmonary embolism are tempered by the modest number of outcome events in the trials and the wide CIs surrounding the point estimates, which do not reliably exclude clinically important differences between the 2 treatments.

Individual studies and meta-analyses of trials that included both patients with deep venous thrombosis and pulmonary embolism have demonstrated that low-molecular-weight heparin is at least as effective as unfractionated heparin for preventing recurrent thrombosis, with no increase in major bleeding events (1, 43–45). Furthermore, the recognition that deep venous thrombosis and pulmonary embolism represent different manifestations of the same underlying disease process (46) suggests that these entities should respond similarly to the same treatment. Nevertheless, many clinicians continue to use unfractionated heparin as first-line therapy for the initial management of patients with pulmonary embolism because of concern about the lack of evidence for the effectiveness of low-molecular-weight heparin for this indication. In this context, our finding that low-molecular-weight heparin is as effective and safe as unfractionated heparin for the treatment of patients with nonmassive pulmonary embolism is reassuring and supports the use of low-molecular-weight heparin as first-line anticoagulant therapy for this indication.

Table 4. **Major and Minor Bleeding during Treatment with Low-Molecular-Weight Heparin or Unfractionated Heparin**

Outcome	Low-Molecular-Weight Heparin Recipients	Unfractionated Heparin Recipients	Odds Ratio (95% CI)
	n/n (%)		
Major bleeding	14/1023 (1.4)	21/928 (2.3)	0.67 (0.36–1.27)*
Minor bleeding	67/982 (6.8)†	48/874 (5.5)†	1.08 (0.73–1.59)‡

* Heterogeneity: chi-square = 5.03.
† Data on this outcome were not available from the study by Decousus et al. (41).
‡ Heterogeneity: chi-square = 12.78.

No difference was observed in fatal outcomes at the end of treatment in patients randomly assigned to low-molecular-weight heparin compared with unfractionated heparin. However, this early estimate was based on only 25 events; by 3 months, more than 100 deaths had occurred and the number of fatal outcomes with low-molecular-weight heparin appeared to be decreased, as had been seen in previous meta-analyses comparing low-molecular-weight heparin with unfractionated heparin for the treatment of deep venous thrombosis or venous thromboembolism (1, 43–45, 47). The mechanism responsible for any reduction in deaths is unclear, although it has been attributed to a differential effect of low-molecular-weight heparin on fatal outcomes in patients who develop venous thromboembolism in the setting of cancer. However, this effect alone does not explain the magnitude of the decrease in mortality rate that has been reported and is not supported by the results of the recently completed Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy in the Long-Term Treatment of Venous Thromboembolism in Patients with Cancer trial, which demonstrated no benefit of long-term therapy with low-molecular-weight heparin compared with warfarin for the

prevention of death in patients with cancer-related venous thromboembolism (48). We could not examine outcomes separately in patients with cancer because these data were neither reported nor available when requested from the investigators in the majority of studies.

Individual preparations of low-molecular-weight heparin differ with respect to their mean molecular weights, ratio of anti–factor Xa to anti–factor IIa activity, and half-life, but it remains uncertain whether they differ in efficacy or safety. Type of low-molecular-weight heparin did not appear to influence estimates of the efficacy or safety of low-molecular-weight heparin compared with unfractionated heparin in our meta-analysis, although this finding may be due to inadequate statistical power because of the relatively small number of trials and large number of low-molecular-weight heparin preparations that were used.

Our study has several limitations. First, the number of patients and the number of outcome events was modest. Therefore, our meta-analysis lacked statistical power to provide precise estimates of incidence and to detect statistically significant and clinically important differences in treatment effect between low-molecular-weight heparin and unfractionated heparin. However, our estimates of treatment effect in patients with symptomatic or asymptomatic pulmonary embolism are consistent with results obtained from individual trials, there was no statistical evidence of heterogeneity for any outcome, and the results of sensitivity analyses did not alter our results. The lack of statistically significant difference between low-molecular-weight heparin and unfractionated heparin is also consistent with results of the most recent meta-analyses evaluating the relative efficacy and safety of these agents in patients with any venous thromboembolism (45, 47). Second, the design of the included studies varied. Differences among trials are inevitable, because individual trials involve different samples with different treatment protocols; heterogeneity always exists, even within individual trials (49, 50). Differences in trial design do not necessarily preclude pooling of their results because in a meta-analysis, individual patients are directly compared only with other patients within the same trial rather than across the trials. Third, we pooled data from subgroups of patients with asymptomatic pulmonary embolism in the context of symptomatic deep venous thrombosis with data from trials that included only patients with symptomatic pulmonary embolism. However, no heterogeneity of treatment effect was seen for any efficacy or safety outcome examined across these 2 groups of trials. Furthermore, although patients who present with asymptomatic pulmonary embolism may be at lower absolute risk for recurrent venous thromboembolism or death than are those who present with symptomatic pulmonary embolism (51), there is no biological, pharmacologic, or clinical reason to expect that the relative efficacy and safety of low-molecular-weight heparin and unfractionated heparin will differ. Therefore, we believe that pooling of data across these trials remains valid. Fourth, suboptimal therapy with unfractionated heparin resulting from failure to use a validated activated partial thromboplastin time therapeutic range has been proposed to account for any apparent inferiority of unfractionated heparin to low-molecular-weight heparin seen in previous meta-analyses (52). Finally, meta-analysis remains retrospective research that is subject to the methodologic deficiencies of the included studies. For example, we cannot exclude publication bias despite the approximately symmetric funnel plots because these plots are difficult to interpret when the number of studies is small. However, we minimized the likelihood of bias by developing a detailed protocol before commencing this study; performing a meticulous and exhaustive search for both published and unpublished studies; and using explicit methods for study selection, data extraction, and data analysis. Furthermore, we considered the totality of the randomized evidence by including all relevant properly randomized trials, and we approached investigators from each study to verify and, if necessary, update the data that were extracted from their trial reports.

A recent trend has been to compare the "net clinical benefit" of antithrombotic therapies by using a composite outcome that includes both efficacy and safety end points (7, 28, 53, 54). We could not perform a similar analysis because data on individual patients, which are required to avoid double counting of end points, were not available. However, separate examination of efficacy and bleeding outcomes in our meta-analysis suggests that low-molecular-weight heparin compared with unfractionated heparin may be associated with a net clinical benefit when used in the initial treatment of pulmonary embolism.

Our data are consistent with the conclusion that low-molecular-weight heparin is as effective and safe as unfractionated heparin for the initial treatment of nonmassive pulmonary embolism. The superior convenience, lower risk for allergy and heparin-induced thrombocytopenia (55), and proven cost-effectiveness of low-molecular-weight heparin compared with unfractionated heparin (3) make it an attractive alternative to unfractionated heparin for this indication. Preliminary data suggest that low-molecular weight heparin may be used for out-of-hospital treatment of patients with nonmassive pulmonary embolism (56–58), but the safety of this approach needs to be further evaluated. The selective factor Xa inhibitor fondaparinux has recently also been shown to be at least as effective and safe as unfractionated heparin for the initial management of symptomatic pulmonary embolism (59). However, the efficacy and safety of fondaparinux compared with low-molecular-weight heparin for patients with pulmonary embolism have not been evaluated.

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Appendix Table. **Measures of Study Quality and Details of Trial Sponsorship**

Trial	Randomization		Double-Blinded*	Patients Lost to Follow-up at 3 Months, *n/n (%)*	Study Sponsor
	Proper Generation of Allocation Sequence	Concealment of Allocation Sequence			
European multicentre study, 1991 (36)	Random number table	Sealed envelopes	No	7/108 (6.5)	Laboratories Sanofi-Choay, Paris, France
Hull et al., 1992 (8, 32)	Computer generated	Yes†	Yes	0	Heart and Stroke Foundation of Alberta, Edmonton, Alberta, Canada; Novo Nordisk, Bagsvaerd, Denmark
Prandoni et al., 1992 (37)	Yes	Sealed envelopes	No	0	Laboratories Sanofi-Choay, Paris, France
Thery et al., 1992 (38)	Yes	Sealed envelopes	No	0	Laboratories Sanofi-Choay, Paris, France
Kuijer et al., 1995 (13)	Computer generated	Sealed envelopes	No	1/67 (1.5)	Pharmacia & Upjohn, Stockholm, Sweden
Meyer et al., 1995 (39)	Computer generated	Sealed envelopes	No	5/48 (10.4)	Pharmacia, St. Quentin en Yvelines, France
Columbus Trial, 1997 (6)	Computer generated	Central telephone	No	0	Knoll AG, Ludwigshafen, Germany
Simonneau et al., 1997 (7)	Computer generated	Central telephone	No	1/612 (0.2)	Leo Pharmaceuticals, St. Quentin en Yvelines, France
Campbell et al., 1998 (40)	Random number table	Yes†	No	0	None
Decousus et al., 1998 (41)	Computer generated	Central telephone	No	0	Bellon Rhône-Poulenc Rorer Laboratories, Montrouge, France
Kirchmaier et al., 1998 (42)	Yes	Central telephone	No	8/80 (10)	Sardoz, Nuremberg, Germany
Merli et al., 2001 (9)	Computer generated	Sealed treatment kits	No	5/287 (1.7)	Aventis Pharmaceuticals, Bridgewater, New Jersey; Aventis Pharma SA, Antony, France

* Patient and investigator.
† Details not available.

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