A Meta-analysis Comparing Low-Molecular-Weight Heparins With Unfractionated Heparin in the Treatment of Venous Thromboembolism

Examining Some Unanswered Questions Regarding Location of Treatment, Product Type, and Dosing Frequency

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Objectives: To compare the efficacy and safety of unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) and to examine current controversies in the treatment of venous thromboembolism (VTE) (ie, setting, product type, and frequency of administration).

Methods: Data were abstracted from MEDLINE, HEALTH, previous reviews, personal files, clinical experts, and conference abstracts. Randomized controlled trials of patients diagnosed with acute VTE that compared LMWHs with UFH were included. Independent duplicate assessment was done for methodological quality and data extraction. Data are reported as pooled relative risks (RRs) and 95% confidence intervals (CIs) comparing LMWHs with UFH as determined by the random effects model.

Results: Thirteen studies were included. There was no statistically significant difference in risk between UFH and LMWHs for recurrent VTE (RR, 0.85 [95% CI, 0.65-1.12]), pulmonary embolism (RR, 1.02 [95% CI, 0.64-1.62]), major bleeding (RR, 0.63 [95% CI, 0.37-1.05]), minor bleeding (RR, 1.18 [95% CI, 0.87-1.61]), and thrombocytopenia (RR, 0.85 [95% CI, 0.45-1.62]). There was a statistically significant difference for risk of total mortality (RR, 0.76 [95% CI, 0.59-0.98]) in favor of LMWHs. Inpatient treatment may reduce the risk of major bleeding vs outpatient therapy. Once-daily therapy is as safe and effective as twice-daily therapy when compared indirectly. Different products could not be statistically compared, but qualitative analysis shows that there are no apparent differences in efficacy and safety.

Conclusions: Low-molecular-weight heparins are at least as effective as UFH in preventing recurrent VTE. It is unlikely that LMWHs are superior in the treatment of VTE, but they do show a statistically significant decrease in total mortality. No differences were seen in the development of recurrent VTE dependent on treatment setting. There were no apparent differences between once-daily and twice-daily therapy or among products. Inpatient therapy may be associated with less major bleeding; therefore, if LMWHs are given in the outpatient setting, patients should be rigorously monitored.

Arch Intern Med. 2000;160:181-188

VENOUS thromboembolism (VTE) is a common and treatable disease that is associated with increased mortality.1,2 Until recently, the standard therapy for VTE has been 5 to 10 days of unfractionated heparin (UFH) followed by at least 3 months of oral anticoagulation.3 Recently, low-molecular-weight heparins (LMWHs), a relatively new class of anticoagulants, have been compared with UFH.3 Low-molecular-weight heparins have theoretical advantages over UFH, including higher bioavailability, longer half-life, and a more predictable antithrombotic effect.5,6 These properties make LMWHs suitable for fixed-dosage, weight-adjusted subcutaneous administration once or twice daily without the need for laboratory monitoring. Furthermore, LMWHs have been shown to be safe and effective for outpatient therapy.5,6,7 Meta-analyses of randomized controlled trials evaluating the treatment of VTE suggest that LMWHs are safer and more effective than UFH.8,9 However, these initially favorable results differ from more recent large studies that showed no significant differences in the efficacy or safety of LMWHs vs UFH.9,10 Therefore, the true relative efficacy and safety of LMWHs compared with UFH remain unknown. The issue is particularly important when considering cost-effectiveness in patients who require in-hospital anticoagulation therapy, such as those with pulmonary embolism (PE) or those with deep vein thrombosis (DVT) who require hospitalization for other reasons.

Our objectives were to update the general question of the relative efficacy of
METHODS

The MEDLINE (1986-1996), HEALTH (1975-1996), and Cochrane Library (1997, issue 1) databases were searched using a comprehensive search strategy for randomized controlled trials along with MeSH and text words, including antiocoagulant therapy, heparin, and LMWHs in their various formulations; thromboembolism; and pulmonary embolism. In addition, the references of previous review articles, files of local thromboembolism experts, and abstracts from recent meetings (ie, the American Heart Association, the American Society of Hematology, and the International Society on Thrombosis and Haemostasis) were reviewed. Each citation was reviewed by 2 reviewers independently who assessed them for inclusion based on a predetermined process and set of criteria. Disagreements were resolved by consensus. Agreement scores were calculated and evaluated at different stages of the process. Revisions in coding definitions and procedures at each stage were made, if needed.

To be included in this meta-analysis, a trial had to meet the following criteria: (1) randomized controlled trial; (2) enroll adult patients with a diagnosis of VTE that was confirmed by the presence of an intraluminal filling defect on contrast venography films, venous noncompressibility on Duplex ultrasonography films taken for acute DVT, the results of a high-probability ventilation-perfusion lung scan, or the presence of an intraluminal filling defect on pulmonary angiography films taken for PE; (3) compare intravenous UFH with subcutaneous LMWHs; and (4) evaluate the outcomes of recurrent VTE (DVT and PE or PE alone) as determined by objective test results and blinded outcome assessment that was confirmed by an independent assessor or adjudication committee, major bleeding, total mortality, or thrombocytopenia. A study was excluded if it was not written in English or French, if data could not be extracted, or if there was no patient follow-up beyond the initial administration of heparin therapy. Trials comparing subcutaneous UFH with LMWHs were also excluded since the current practice in North America is to administer UFH by continuous infusion. Recurrent DVT involving the calf or more proximal veins had to be diagnosed by a new intraluminal filling defect on venography, a new noncompressible vein segment on ultrasonography, or, if these were inconclusive, a new abnormal impedance plethysmography test result was considered acceptable. The diagnosis of recurrent PE required the results of a new high-probability ventilation-perfusion lung scan, the presence of a new intraluminal filling defect on pulmonary angiography, or the demonstration of associated new DVT by either compression ultrasonography or venography. The outcome of recurrent VTE was calculated by combining the number of patients with recurrent DVT and PE.

A study was classified as providing outpatient therapy if some of the patients who were allocated to receive LMWHs were treated as outpatients. Bleeding and thrombocytopenia were classified according to the criteria listed by the authors. All bleeding events that were not classified as major were considered minor.

Methodological quality was assessed using criteria adapted from published sources. Methodological quality assessment and data extraction were done independently and in duplicate. Discrepancies were resolved by review of the original study.

The primary analysis was the comparison of therapy with UFH vs LMWHs, including patients presenting with DVT or PE. A priori, potential secondary analyses were identified: 7 potential secondary analyses were methodologically in nature (eg, blinded outcome analysis or financial support) and 10 were clinical in nature (eg, early vs late recurrence of thromboembolism or adjusted-dosage UFH or not). These potential secondary analyses were evaluated for rationale and supportive evidence and then rated independently by clinical experts according to clinical importance and relevance. Those with the highest rating formed the basis for the 3 subgroup analyses presented. Based on this selection process, the following secondary analyses were performed: (1) once-daily vs twice-daily treatment regimen, (2) inpatient vs outpatient treatment location, and (3) comparisons of individual LMWHs.

Agreement between 2 independent reviewers was calculated using the κ statistic. A κ of 0.9 or greater indicated excellent agreement and required no revisions to the process. The differences between LMWHs and UFH were summarized using a combined relative risk (RR) for meta-analysis, which is the weighted average of the RRs from each study; the risk of LMWHs relative to UFH is reported. The value reported indicates the risk of the outcome while receiving LMWHs as a percentage of the risk of the event while receiving UFH (for example, 0.4 indicates that the risk of obtaining the outcome while receiving LMWHs is 40% that of UFH). To determine the statistical significance and to assist in determining the clinical importance of the results, 2-sided P values and 95% confidence intervals (CIs) were determined. The model of random effects was used; χ² tests for heterogeneity were also calculated. Data were analyzed according to the principle of intention to treat. Weighted least squares linear regression was used to determine statistically significant differences between subgroups. The dependent variable was the individual study RR. Weights were the components of variance owing to interstudy variation in effect size as determined using the random effects model. The coefficient slope of the heparin type X subgroup factor was examined to detect a significant difference in the linear relationship formed by the data generated from one subgroup compared with another.

LMWHs vs UFH and to address the following questions that remain unanswered: Is outpatient therapy with LMWHs as effective and safe as inpatient therapy with LMWHs? Is once-daily therapy with LMWHs as effective and safe as twice-daily therapy with LMWHs? Are there differences in effectiveness and safety among different LMWH preparations?

In order to answer these questions, we performed a meta-analysis.

RESULTS

From 775 articles screened, 33 articles were identified as randomized controlled trials comparing LMWHs and
UFH and were included for data extraction. Of these, 20 articles were excluded; the remaining 13 studies were included in this meta-analysis. Articles were excluded for the following reasons: subcutaneous UFH was compared with subcutaneous LMWHs (n = 7), intravenous UFH was compared with intravenous LMWHs (n = 2), data could not be extracted (n = 3), the abstract did not provide sufficient data (n = 2), the study was not a randomized trial (n = 1), patients were not reexamined beyond the initial administration of heparin therapy (n = 2), the article could not be retrieved (n = 1), and it was unclear if there was a blinded outcome assessment (n = 1).

Various aspects of methodological quality were evaluated. Six (46%) of the 13 studies reported an acceptable method of randomization. Only 1 study reported a double-blind method and therefore also had a treatment group that was blinded to the treatment received after it was allocated. Allocation to the study arms was concealed prior to randomization in 7 (54%) of 13 studies. All but 1 study reexamined over 90% of the patients who were enrolled. This meta-analysis includes 883 patients who initially presented with PE (20% of total patients enrolled). All 13 studies that were included also assessed the incidence of recurrent VTE. Analysis of the pooled RR yielded a nonsignificant result of 0.85 (95% CI, 0.65-1.12) when comparing LMWH with UFH. None of the individual RRs was statistically significant in the primary studies; 7 of the point estimates were in favor of LMWH and 6 were in favor of UFH. For the outcome of PE alone (as a manifestation of recurrence), analysis of the pooled RR yielded a nonsignificant result of 1.02 (95% CI, 0.64-1.62) when comparing LMWH with UFH.

All studies involved adjustment of treatment with UFH to a specified target-activated partial thromboplastin time range, and all patients received either LMWH or UFH for at least 5 days. The maximum duration of injectable anticoagulant administration was 10 days. Oral anticoagulation with a coumarin derivative was initiated on day 1 to day 10 after initiation of the injectable heparin; in the majority (69%) of studies, it was initiated within 48 hours of presentation, although in 2 studies oral anticoagulation was begun on day 7 or day 10. The mean age of treated patients ranged from 57 to 67 years and the percentage of male patients ranged from 43.8% to 61.2%. Eight of 13 trials included patients with only proximal DVT or PE, while the other 5 also enrolled patients with distal DVT. The anticoagulant regimens used are presented in Table 1. Event rates for selected outcomes are provided in Table 2.

All 13 studies that were included assessed the incidence of recurrent VTE (Table 3, Figure 1). Analysis of the pooled RR yielded a nonsignificant result of 0.85 (95% CI, 0.65-1.12) when comparing LMWH with UFH. None of the individual RRs was statistically significant in the primary studies; 7 of the point estimates were in favor of LMWH and 6 were in favor of UFH. For the outcome of PE alone (as a manifestation of recurrence), analysis of the pooled RR yielded a nonsignificant result of 1.02 (95% CI, 0.64-1.62) when comparing LMWH with UFH (12 studies). Again, none of the individual RRs was statistically significant in the primary studies.

All 13 studies that were included also assessed the incidence of major bleeding. Analysis of the pooled RR yielded a nonsignificant result of 0.63 (95% CI, 0.37-1.05) when comparing LMWH with UFH. The combined analysis for minor bleeding included 12 of the 13 studies and produced a nonsignificant pooled RR of 1.18 (95% CI, 0.87-1.61).
The analysis of total mortality produced a statistically significant pooled RR of 0.76 (95% CI, 0.59-0.98) in favor of LMWH or a 24% reduction in risk of total mortality for LMWH vs UFH. This was based on information that was available from 10 of 13 studies. While no individual study produced a statistically significant result in favor of LMWH, 9 of the 10 studies exhibited a trend in favor of LMWH. The pooled analysis yielded a nonsignificant RR of 0.85 (95% CI, 0.45-1.62) for the incidence of thrombocytopenia. No statistically significant heterogeneity was found for any of the primary analyses.

Three studies were considered to be outpatient therapy trials. Inpatient LMWH therapy was associated with fewer major bleeding events than outpatient LMWH administration (Table 4 and Figure 2). All other indirect comparisons produced nonsignificant results.

Five of 13 studies involved once-daily LMWH administration. The analysis of studies using twice-daily vs once-daily dosing is presented in Table 5 and Figure 3. Pooled trials administering once-daily LMWH, compared with those administering twice-daily dosing, did not produce a statistically significant difference for any outcomes that were analyzed. No results were significant for LMWH vs UFH or notably different between subgroups.

Five different LMWH products were administered across the 13 included studies (Table 6 and Figure 4).
The differences between these groups were not tested statistically, since it was felt that there were too few studies that administered each LMWH product to generate useful results. In all but 1 analysis (the relative effect of nadroparin compared with UFH in the production of major bleeding episodes), the CIs overlap the value of 1.0, signifying no statistically significant difference in relative benefit or risk between each LMWH product and UFH. No significant heterogeneity was found for any of the secondary analyses.

**COMMENT**

Three previous meta-analyses comparing treatment with LMWHs and UFH have been published; in 2 of these reports, the incidences of recurrent VTE and major bleeding were significantly reduced in patients who were treated with LMWHs, while in the third, nonsignificant trends favoring treatment with LMWHs were seen. The results of the current meta-analysis, which includes more than twice as many patients as the previous meta-analyses, show no statistically significant differences between LMWHs and UFH in effectiveness, incidence of major or minor bleeding, or thrombocytopenia.

Consistent with a previous meta-analyses, our meta-analysis showed a significant difference in total mortality in favor of LMWHs (RR, 0.76 [95% CI, 0.59-0.98]). None of the RRs from any of the studies included was statistically significant, although most showed a trend in favor of LMWHs. The reason for this observation remains unexplained because we are unable to show a reduction in fatal PE as an explanation. One hypothesis is that UFH is associated with a relatively higher death rate compared with LMWH when higher dosages of UFH are administered. In support of this theory, studies that produced approximately twice as many deaths in patients receiving UFH vs LMWH used UFH dosing protocols that allowed for the initial administrations of 35 000 to 40 320 IU of UFH per 24-hour period. Studies with lower relative total mortality rates (range, 0.66-1.50) used UFH dosing protocols of between 20 000 and 32 500 IU per 24-hour period.

Another hypothesis generated in previous meta-analyses was that LMWHs may reduce mortality in a subgroup of patients with cancer, which is consistent with evidence demonstrating that LMWHs may have an antitumor effect. This hypothesis should be tested prospectively in a large clinical trial.

No difference in the incidence of patients experiencing thrombocytopenia was found between UFH and LMWHs. However, it is unclear whether the events reported in the individual studies represent true heparin-induced thrombocytopenia. The definition of thrombocytopenia was either not provided or stated as a drop in platelet count below $50 \times 10^9/L$ (or $100 \times 10^9/L$ if clinical symptoms were present). Confirmatory heparin-dependent IgG antibody testing was not performed in any studies. Therefore, these event rates cannot be used as an indicator of the more clinically relevant type 2 heparin-induced thrombocytopenia.

This meta-analysis suggests that there is no difference in the risk of recurrent VTE between inpatient and outpatient treatment with LMWHs, but that inpatient treatment with LMWHs may be associated with less major bleeding compared with outpatient treatment. The rates of major bleeding in the UFH treatment arms are similar between inpatient and outpatient trials, as shown in Table 2; therefore, this is not a likely explanation for the differences. Patients receiving therapy in the outpatient setting, who are probably not accustomed to self-administration and monitoring of injectable therapy, may be less able to perform this self-care accurately or recognize the initiation stage of an adverse event, placing...
The analysis of once-daily vs twice-daily dosing of LMWHs suggests that the former, which is more feasible in the outpatient setting, is at least as effective as twice-daily dosing in preventing thromboembolic recurrences and results in no difference in the incidence of major bleeding events or overall mortality. This finding is consistent with a recent randomized double-blind study comparing once-daily with twice-daily nadroparin therapy that showed an absolute difference of 3.1% (95% CI, −6.6% to 0.5%) in favor of once-daily therapy.57

Five LMWH products were compared with UFH among the 13 included studies. Based on the pooled results, there are no major differences among preparations. This suggests that the use of any of the products in the dosages evaluated in the trials is reasonable. However, this conclusion is limited and must be tempered by the fact that the comparison of LMWH products is indirect; until studies that directly compare different LMWH preparations for the treatment of VTE are performed, it is impossible to make definitive conclusions about their relative safety and efficacy. In addition, there is variability in the anti–factor Xa to anti–factor IIa ratios among LMWHs and in their half-lives.58,59 These differences underline the fact that these preparations are biologically different and therefore might differ in efficacy and safety, although no striking differences were noted in this overview.

There are several limitations of this meta-analysis that should be addressed. First, only English- and French-language studies were screened. This might have generated a publication bias, since studies in other languages may be available that could contribute to these results.60 Second, since we used subgroup analyses to compare information across studies, there may be interstudy variability that has not been accounted for in these comparisons. This is an inherent, unavoidable weakness in the method of meta-analysis. However, since the subgroups were stated a priori and were based on a biological rationale, no heterogeneity of studies was found, and the information used was derived from studies of a high and similar methodological quality, the potential for bias is limited. Furthermore, no attempt was made to combine estimates from each subgroup to create an overall numerical estimate, as these results would lose the power of randomization. Instead, the results were compared qualitatively for strength of relationship, consistency of relationship, biological plausibility, and statistical significance of the relationship,61 and the results were assessed quantitatively using regression techniques to determine if there were significant differences among subgroups.

Third, our analysis of the location of treatment was limited by the definition used to classify studies. Our definition was very liberal, since it defined a study as outpatient if it was the intention of the authors to treat at least some of the patients in this manner. The percentage of patients who were fully treated as outpatients in each of the 3 studies was 48.6%,7 36%,6 and 27%,33 respectively. Because of the relatively small number of patients who were truly treated as outpatients in the studies that we labeled as outpatient studies, the true RRs in clinically important outcomes may have been diluted.

The studies that were included to answer the primary question of this meta-analysis were systematically determined to have high methodological quality and clinical similarity, since all were randomized controlled trials evaluating similar treatments for patients with similar clinical conditions. Therefore, the results generated would be classified as level 1 evidence.62 The number of studies that were available to examine the remaining questions of location of treatment, product type, and dosing frequency of LMWHs is small. Indirect comparisons were used owing to the lack of studies that were available to provide direct comparisons to evaluate these issues. However, these are the only studies known to be available; thus, these are the studies that will be used by practitioners and policy makers to make decisions.
In order to justify an alteration in practice patterns, the change must be shown to be more effective than the current standard, or if equivocal, it should cause less harm, be more convenient, or be less expensive. The results of this analysis indicate that LMWHs are at least as effective as UFH in preventing recurrent VTE, but that LMWHs are unlikely to be superior. For patients with an initial diagnosis of either DVT or PE, LMWHs are a reasonable option. For patients who require treatment in hospital, LMWHs are a reasonable therapeutic option. However, depending on perspective (eg, drug costs, nursing time, and resource utilization), LMWHs may not be cost-effective. In suitable patients, LMWHs offer the advantage of outpatient treatment, which is likely to reduce health care costs. It appears that once-daily LMWH administration is as safe and effective as twice-daily administration, and that use of any of the LMWH preparations is reasonable, provided they are used in dosages that have been used in the aforementioned clinical trials. Further studies should be done to determine whether different LMWHs have different safety and efficacy profiles and to directly compare once-daily with twice-daily dosing.

Accepted for publication March 25, 1999.

Although this project did not have any direct financial support, Dr Dolovich was the recipient of a fellowship from the Canadian Society of Clinical Pharmacology, Toronto, Ontario; Dr Ginsberg is a recipient of a research scholarship from the Heart and Stroke Foundation of Ontario, Toronto; and Dr Holbrook is the recipient of a research personnel award from the Ontario Ministry of Health, Toronto.

An earlier version of part of this work was published as Dolovich L, Ginsberg JS. Low molecular weight heparins in the treatment of venous thromboembolism. Vessels. 1997;3:4-11.

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