Should Low-Molecular-Weight Heparins Replace Unfractionated Heparin as the Agent of Choice for Adults with Deep Venous Thrombosis?

Dan Brewer, MD
Knoxville, Tennessee

BACKGROUND. Several low-molecular-weight heparins (LMWHs) are now approved for use in the United States for the prophylaxis of venous thromboembolism. They are used in Europe for the treatment of deep venous thrombosis (DVT) and pulmonary embolism. This review examines the evidence addressing the question "Should LMWHs replace unfractionated heparin (UFH) in the treatment of adults with DVT?"

METHODS. We performed a MEDLINE search using the key words "low-molecular-weight heparin" from the years 1990 to 1998, and the results were assessed using the JAMA Users' Guides to the Medical Literature system.

RESULTS. Low-molecular-weight heparins are at least as safe and effective as unfractionated heparin in the treatment of patients with DVT. They are probably more effective and safer. They are more convenient to use and are associated with lower overall costs.

CONCLUSIONS. Based on efficacy, safety, convenience, and cost, LMWHs are clearly superior to UFH in the treatment of DVT in primary care. Studies that confirm an expected improvement in patient-oriented outcomes (eg, mortality and quality of life) need to be done.

KEY WORDS. Low-molecular-weight heparin; heparin; deep venous thrombosis; pulmonary embolus. *(J Fam Pract 1998; 47:185-192)*

CLINICAL QUESTION Should low-molecular-weight heparins replace unfractionated heparin as the treatment of choice for adults with DVT?

Heparin has been the standard agent for acute anticoagulation for more than half a century.[1] Clinical trials have shown that it is effective in preventing thromboembolism in high-risk medical and surgical patients, and in the treatment of established thromboembolism. It is also widely used in conditions for which the evidence of efficacy is less certain, including acute stroke[2] and myocardial infarction.[3] In spite of its established effectiveness, there are persistent problems with safety, adverse effects, and the inconvenience of monitoring the anticoagulant effect.

Unfractionated heparin is a heterogeneous mix of polysaccharide chains ranging in molecular weight from 3000 to 30,000 daltons. Low-molecular-weight heparins (LMWH) are fragments of unfractionated heparin that are produced by depolymerization and vary in molecular weight from 4000 to 6000 daltons. They were first formulated in the 1970s and have been studied in humans since the early 1980s. Their homogenous mix of heparin chains produces a more predictable anticoagulant response because of better bioavailability, longer half-life, and dose-independent clearance. These pharmacologic advantages over unfractionated heparin (UFH) predict clinical advantages in the prophylaxis and treatment of deep venous thrombosis (DVT).[4] These advantages are listed in Table 1.

LMWHs have been used clinically as prophylaxis for DVT in Europe since the 1980s and in America since the US Food and Drug Administration (FDA) approval of enoxaprin in 1993. There are now four LMWHs approved for use in the United States, although they have been approved by the FDA only for prophylactic use. They are used for the treatment of DVT and pulmonary embolus (PE) in Europe. LMWHs are now considered the preferred agent for prophylaxis in orthopedic surgery and appropriate for prophylaxis in general surgery.[5] They have also been studied as prophylaxes in patients with high-risk general medical conditions,[6,7] stroke,[8] trauma,[9] vascular surgery grafts,[10] and acute spinal cord injuries.[11] LMWHs have been studied for the prevention of postangioplasty stenosis.[12] They have also been studied for the treatment of unstable angina[13] and acute stroke.[14]

This review will focus on the evidence comparing LMWHs with UFH in the treatment of established DVT and will attempt to answer the question: Should LMWHs replace UFH as the treatment of choice for adults with DVT? The criteria for making this decision include the prevention of recurrent thrombosis, the reduction of morbidity and mortality, and treatment costs.

METHODS

Electronic MEDLINE searches for the years 1990 to 1998 were performed with the *Grateful Med* search engine and the National Library of Medicine's *PubMed* search engine

Submitted, revised, May 1, 1998.
From the University of Tennessee Medical Center. Requests for reprints should be addressed to Dan Brewer, MD, Department of Family Practice, 1924 Alcoa Highway, Knoxville, TN 37920. E-mail: dbrewer2@UTK.edu

TABLE 1

Potential Advantages of Low-Molecular-Weight Heparins (LMWHs)

Basic science research findings

LMWHs bind less to heparin-binding proteins.
LMWHs bind less to endothelial cells and matrix proteins.
LMWHs bind less to platelets.

Disease-oriented evidence

LMWHs have more predictable dose response curves and better bioavailability. Laboratory monitoring not required.
LMWHs have a longer half-life which allows dosing once or twice daily.
LMWHs produce less bleeding for a given antithrombotic effect.
LMWHs cause fewer antiplatelet antibodies.

Patient-oriented events

Outpatient treatment
LMWHs are associated with fewer thromboembolic complications from inadequate treatment.
LMWHs cause less major bleeding.
LMWHs cause less heparin-induced thrombocytopenia.

using the MeSH heading "low-molecular-weight heparin." The searches were limited by specifying human trials in the English language. All meta-analyses, practice guidelines, and randomized clinical trials found by the search were collected, and those investigating the treatment of acute DVT were analyzed. An Internet search for information on analyses of LMWHs was also performed using evidence-based medicine sources.*

Initially, each appropriate meta-analysis and practice guideline retrieved was evaluated for validity using the appropriate Users' Guide to the Medical Literature.[15,16] All randomized controlled trials involving a comparison of LMWHs with UFH that were not included in the previously retrieved meta-analyses were then evaluated for validity[17] and compared with the conclusions of the meta-analyses and practice guidelines. Formal meta-analytic statistical analysis was not done.

Appropriate articles that might have been missed in the original searches were found by evaluating the bibliographies of the retrieved randomized clinical trials and meta-analyses, as well as the editorials and review articles found by the search. No attempt was made to contact authors or pharmaceutical companies directly to look for unpublished trials, although this was done by the original authors of each meta-analysis discussed in this review.

* The Internet search included the Web sites for Bandolier (www.jr2.ox.ac.uk/bandolier), the Centre for Evidence-Based Medicine (www.cebm.jr2.ox.ac.uk/CEBM), The Journal of Family Practice (www.jfp.msu.edu), and the American College of Physicians Journal Club (www.acponline.org/journals/acpjc). The Cochrane database (issue 4, 1997) on CD-ROM was also searched for reviews on LWMHs.

RESULTS

Five formal meta-analyses and one practice guideline were found that included analyses of the randomized clinical trials published through 1994. Six randomized clinical trials were found that were published after 1994. The Cochrane Database has an ongoing protocol entitled "Low-Molecular-Weight Heparins in the Treatment of Venous Thromboembolism,[18] due for publication as a completed review in late 1998.

META-ANALYSES

Leizorovicz published a 1996 meta-analysis[19] that updated his earlier publication of 1994.[20] The two meta-analyses published by the Siragusa/Hirsch group from Hamilton, Ontario, and Pavia, Italy,[21,22] use the same strategies and statistics and are considered a single study for the purposes of this review. Therefore, the five meta-analyses found in this search are treated as three rather than five separate studies. Summaries of the meta-analyses are presented in Tables 2 and 3.

Lensing et al[23] identified 19 randomized clinical trials published between 1984 and 1994, and found that 10 of them fulfilled their criteria for validity. They eliminated studies for inadequate randomization, for not having blinded, objective end points, and for using LMWH doses larger than those in current use. They concluded that low-molecular-weight heparins administered subcutaneously in fixed doses adjusted for body weight and without laboratory monitoring are more effective and safer than adjusted-dose heparin."

Leizorovicz et al[20] looked at all randomized controlled trials comparing LMWHs with UFH in the treatment of DVT and found 16 studies for their initial analysis. This included five studies using high-dose subcutaneous UFH that were excluded from Lensing's meta-analysis. The 1996 update analyzed 20 studies and included four of the six trials listed in Table 4 and Table 5 that are not found in the earlier meta-analyses.[25,26,27,28] Leizorovicz and colleagues concluded that "low-molecular-weight heparins seem to have a higher benefit/risk ratio than unfractionated heparin in the treatment of venous thrombosis."

The Siragusa/Hirsch group[21,22] found 13 studies that met their inclusion criteria and then divided them into level 1 studies (double-blind or blinded outcome assessment) and level 2 studies (all others). They conducted individual statistical analyses of each group and of all the studies together. Evaluation of the level 1 studies showed an advantage of LMWH over UFH in both efficacy and safety, but the level 2 studies and the composite data showed nonsignificant trends in that direction. These investigators concluded that "a conservative interpretation of the results of our meta-analysis is that

unmonitored LMWH is at least as effective and safe as UFH in the treatment of patients with venous thromboembolism. A more probable interpretation is that LMWHs are more effective and safer than UFH in the treatment of DVT."

Table 2 shows the results of the validity assessment for the meta-analyses. Each of them is shown to have acceptable methodology in this analysis. The study by Leizorovicz et al[20] was the broadest study with the most lenient validity criteria for inclusion into the meta-analysis. It included trials that allowed high-dose subcutaneous UFH and trials that used plethysmosgraphy as their primary outcome measure, which the other two meta-analyses excluded. The level 1 analysis by Siragusa and colleagues was the most rigorous and exclusive study, and included only the highest quality trials. Its strict criteria meant that only three studies were included with a total of only 736 patients in the efficacy analysis and 797 in the safety analysis.

Practice Guidelines

The American College of Chest Physicians (ACCP) published its most recent consensus guideline on antithrombotic therapy in 1995.[24] The rules of evidence and recommendation are clearly laid out by this panel and are often cited as a model for evidence-based guidelines. It adheres closely to the format suggested by the JAMA Users' Guide to Practice Guidelines.

The ACCP document notes that LMWHs have not yet received regulatory approval for the treatment of established venous thrombosis in the United States, and it does not, therefore, make a specific recommendation for or

TABLE 2

Validity Assessment of Meta-Analyses of LMWHs and UFH

Criterion	Siragusa/Hirsch[21]	Leizorovicz[19]	Lensing[23]
Did the overview address a focused question?	Yes Reliable estimates of the LMWH and UFH	Yes Whether treatment with hemorrhage, and extension of thrombus more than UFH	Yes Relative efficacy and safety of treatment of DVT
Were the criteria used to select articles for inclusion appropriate	Yes Patients with first DVT, objectively confirmed Randomized comparison of LMWH and UFH Objective outcome measure	Yes Randomized trials comparing LMWH with UFH in treatment of DVT	Yes Randomized trials comparing LMWH and UFH using adjusted dosing
Is it likely that important relevant studies were missed?	Yes Clearly described search strategy and contact of authors for possible unpublished studies	Yes Same	Yes Same
Was the validity of the included studies appraised?	Yes Each study assessed with explicit criteria and labeled as level 1 (blinded outcome assessment) or level 2	No Particularly, there is no assessment of the blinding of the studies. Broader dosing allowed than in others	Yes Excluded for: poor randomization unadjusted UFH no independent outcome assessment
Were assessments of studies reproducible?	Yes Extracted independently by two investigators	Yes Extracted independently by three authors in 1994, but only the single author in the update	Can't tell
Were the results similar from study to study?	Yes Statistical analysis for heterogeneity	Yes Same	Yes Same

Adapted from Oxman et al for the Evidence-Based Working Group.[15]
LMWH denotes low-molecular-weight heparin; UHF, unfractionated heparin; DVT, deep venous thrombosis.

TABLE 3

Results of Meta-Analyses of LMWHs and UFH

Authors of Original Meta-Analysis	# of trials		Thromboembolic Complications	Major Bleeding	Mortality
Leizorovicz[19]	20	RR*	0.77†	0.59‡	0.70
		CI	[0.55-1.08]	[0.35-0.98]	[0.50-0.98]
		ARR	1.4%	1.6	1.7
Siragusa/Hirsch[21]	13§	RR*	0.39	0.42	0.51
		CI	[0.3-0.8]	[0.2-0.9]	[0.2-0.9]
		ARR	3.7%	3.7	2.6
Lensing[23]	10	RR*	0.53	0.68	0.47
		CI	[0.18-0.73]	[0.31-0.85]	[0.10-0.69]
		ARR	3.5%	2.3	3.2

LMWH denotes low-molecular-weight heparin; UHF, unfractionated heparin; RR, relative risk; CI, confidence interval; ARR, absolute risk reduction.
* <1 favors LMWH
†Not statistically significant, P=0.13.
‡0.14 with once daily dosing.
§Thirteen studies included but separate analysis for level 1 (double-blinded) studies and level 2 (all others). Results reported here are for level 1 studies.

against their use for that purpose (although individual clinicians are allowed to use FDA-approved medications for uses other than those that have received regulatory approval). It notes that current data suggest LMWH is as effective and safe as continuous IV heparin but cautions that most conclusions are based on venographic observations rather than clinical outcomes. One recommendation states, "In many countries, LMWH is used in place of unfractionated heparin. Dosing requirements are individualized for each product. LMWH should be administered for 5 to 10 days and therapy overlapped with oral anticoagulation."

Randomized Clinical Trials

Five randomized clinical trials comparing LMWH with UFH in the treatment of DVT[25,26,27,29,30] and one trial in the treatment of PE[28] have been published since 1994. Four of these trials were included in Leizorovicz's 1997 update but were not included in the other reviews. Two of these compared the use of home-based subcutaneous LMWH with traditional hospital-based adjusted-dose UFH.[29,30] There was also one trial that addressed the incidence of heparin-induced thrombocytopenia using UFH and LMWH.[31] Summaries of the validities and results of the six trials are given in Tables 4 and 5.

The studies by Feissinger et al[25] and Luomanmaki et al[26] are randomized trials that compared an LMWH (dalteparin) and UFH in treatment of DVT, with standardized scores of follow-up venography as primary end points. The clinical end points of symptomatic recurrence, bleeding and death were tabulated as secondary end points. These points were rigidly defined and blindly assessed, but both studies were designed with power calculations based on the venography scores, not the clinical end points. In both cases there was a trend, though not a clinically significant one, toward better efficacy and safety with LMWH.

The study published in 1997 by the Columbus investigators[27] compared an LMWH (reviparin) with UFH in the initial treatment of DVT and looked at the clinical end points of symptomatic recurrence, major bleeding, and death. Patients with associated PE or prior venous thrombosis were not excluded. This study of 1000 patients was designed to demonstrate a possible absolute risk reduction of three percentage points in these outcomes. Instead it showed that treatment with LMWH and UFH were equivalent, with no significant differences between the treatment groups in any of the three outcome measures.

The THESEE study group[28] compared an LMWH (tinzaparin) with UFH in the treatment of patients with PE. The combined clinical end points of symptomatic recurrent PE, death, or major bleeding were evaluated. They also looked at the secondary end point of scintigraphically detectable pulmonary vascular obstruction after 8 to 11 days of treatment. This study showed no difference between the two treatment groups, but the authors noted that the patients had a much lower rate of clinical events than their a priori calculations had predicted.

Levine et al[29] and Koopman et al[30] compared inpatient treatment with UFH with outpatient treatment with LMWHs (enoxaparin and nadroparin, respectively) in the treatment of DVT. Both studies excluded patients with PE. Neither study used exclusive outpatient treatment in the LMWH group. Thirty-six percent of the patients in the Koopman study and 49% of the patients in the Levine study were never admitted to the hospital. The LMWH groups had mean lengths of stay of 1.1 days and 2.7 days, compared with 6.5 days and 8.1 days for the UFH groups. Both studies looked at the clinical outcomes of symptomatic recurrence of DVT, bleeding, and death. The Koopman study also looked at measures of quality of life and cost. Neither study showed a significant difference in the rate of clinical end points between the two treatment groups.

In the Koopman study, both groups showed improved quality-of-life with treatment, but the LMWH group

showed better physical activity and social functioning on quality of life subscales. The LMWH group used fewer hospital resources but more outpatient resources. A formal cost analysis was not reported.

SAFETY

Warkentin and colleagues[31] performed a trial comparing the rates of heparin-induced thrombocytopenia in patients receiving enoxaparin (an LMWH) and UFH following elective hip surgery. The incidence of heparin-induced thrombocytopenia was 3% in the patients receiving UFH, but there were no patients receiving the LMWH in whom heparin-induced thrombocytopenia developed. This 3% incidence with UFH is consistent with other prospective trials of UFH. It was also noted that heparin-induced thrombocytopenia is a highly thrombotic state: 8 of 9 patients with heparin-induced thrombocytopenia subsequently were found to have venous thrombosis (odds ratio = 37). Patients with heparin-induced thrombocytopenia should not, however, be treated with LMWH, since there is cross-reactivity to the antibodies believed responsible for the majority of cases.

Several authors have suggested that LMWH is less likely than UFH to cause osteoporosis when used long-term but this has been studied in very few patients.[32] LMWHs ow do not cross the placenta and may be safe for use in pregnancy,[33] but randomized trials have not been performed in this setting.

In December of 1997 the FDA issued a public health advisory on reports of epidural and spinal hematomas with the concurrent use of LMWH and spinal/epidural anesthesia or spinal puncture. The majority of these patients were elderly women undergoing orthopedic surgery.

DISCUSSION

There is a clear consensus among the articles cited that LMWHs are at least as effective and safe as UFH. They are more convenient than UFH, since they can be given once or twice daily by subcutaneous injection without the need

TABLE 4

Validity Assessment of Randomized Clinical Trials of LMWHs vs UFH

	Columbus[27]	Feissinger[25]	Luomanmaki[26]	Levine[29]	Koopman[30]	Simmoneau[28]
Primary Guides						
Was assignment of patients random?*	Yes	Yes	Yes	Yes	Yes	Yes
Was follow-up complete?	Yes 100% at 12 weeks	Yes 231/268 at 6 months	Yes 200/248 at 6 months	Yes 100% at 3 months	Yes 396/400 at 24 weeks	Yes 608/612 at 90 days
Intention-to-treat analysis?	Yes	Yes	Yes	Yes	Yes	Yes
Secondary Guides						
Was there adequate blinding?†	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar?	Yes UHF: 62 years old 20% surgery LMWH: 59 years old 32% surgery	Yes	Yes UFH: 15% CA LMWH: 6% CA	Yes LMWH: 21% prior DVT 19% CA UFH: 14% prior DVT 23% CA	Yes	Yes
Were the groups treated in the same manner?	Yes	Yes	Yes	Yes	Yes	Yes

Adapted, with permission, from Guyatt et al for the Evidence-Based Medicine Working Group.[17]
LMWHs denotes low-molecular-weight heparin; UHF, unfractionated heparin; CA, cancer.
* All studies had central randomization by computer algorithm.
† None of the studies had blinded treatment but all had objected criteria for end points and all end points were assessed by a blinded central committee.

TABLE 5

Results of Randomized Clinical Trials of LMWH Compared with UFH Since 1994

Study	No. of Patients	Agent	Recurrence,% LMWH/UFH	Bleeding,% LMWH/UFH	Mortality,%* LMWH/UFH
LMWH vs UFH for DVT					
Columbus[27]	1021	Reviparin	5.3/4.9	3.1/2.3	7.1/7.6
Feissinger[25]	253	Dalteprin	3.3/1.5	0/1.5	0.8/2.9
Luomanmaski[26]	200	Dalteprin	3.1/1.9	6/6	1/5
LMWH vs UFH for pulmonary embolism					
Simmoneau[28]	612	Tinzaparin	1.6/1.9	2.0/2.6	3.9/4.5
LMWH (outpatient) vs UFH (inpatient)					
Levine[29]	500	Enoxaprin	5.3/6.7	2.0/1.2	4.5/6.7
Koopmann[30]	400	Nadroparin	6.9/8.6	0.5/2.0	6.9/8.1

LMWH denotes low-molecular-weight heparin; UFH, unfractinated heparin.
All paired statistics in this table are not significant.
* 6-months mortality for Feissinger, Koopman, and Luomanmaki; 3-months for Columbus, Levine and Simmoneau.

for activated partial thromboplastin time monitoring of the anticoagulant effect. The possibility of outpatient treatment of uncomplicated DVT would also be a significant advantage of LMWH. The recent randomized controlled trials cited in this paper are all consistent with these conclusions.

None of the individual trials that have been completed have adequate statistical power to show significant differences in safety or mortality.[19] The available meta-analyses are necessary to answer the question of comparative effectiveness and safety until a larger clinical trial is completed.

Each of the meta-analyses shows that LMWH is safer or more effective than UFH. These conclusions are based on recurrent thrombosis or venographic changes in thrombus as the end points of effectiveness. Since UFH is a very effective antithrombotic agent, it is not surprising that the current evidence is not adequate to show a clear advantage of LMWH for more patient-oriented outcomes such as fatal PE. One author calculated that a study would require 10,000 patients to be treated to show a difference in the rate of recurrent PE.[28]

In studies that have looked at mortality rates, there has been an intriguing but difficult to explain reduction in overall mortality in medical patients treated with LMWH as compared with those treated with UFH. This difference has been mostly confined to cancer patients in whom DVT develops, and some authors have speculated that it may be related to undiagnosed thromboembolic events.[22]

Several published cost-analyses comparing LMWHs with UFH in the prophylaxis of DVT in surgical patients have shown LMWHs to be superior in orthopedic patients but not in lower-risk general surgery patients.[34] One Canadian study has addressed the cost-effectiveness of treatment of DVT.[35] Even without considering the possible impact of outpatient treatment using LMWHs, this analysis showed them to be more cost-effective than UFH from the perspective of a single third-party payer. According to Dr R. Light, Medical Director of Cigna Medicare Carrier, the use of outpatient LMWH in America for the treatment of DVT in elderly patients may have the effect of shifting the cost of the medication from the inpatient diagnosis-related group payment by Medicare onto the patient. The wholesale price of 7 days of enoxaparin (1 mg/kg twice daily) for a patient weighing 70 kilograms is approximately $560.36

One survey showed that 60% of all DVT patients referred to a Canadian hospital thrombosis unit would be eligible for outpatient therapy.[37] This suggests a potential for huge cost savings in the United States, where more than 300,000 patients are hospitalized each year with DVT.[38] Only 36% of the patients in the LMWH arm of the trial by Koopman et al[30] were actually treated entirely as outpatients, however, and this represents only 10% of all the patients with DVT who were initially screened for the study.

Unfractionated heparin is much less effective for the treatment of DVT when the therapeutic level of anticoagulation is not reached within the first 12 to 24 hours of treatment.[39] Even in controlled clinical trials with careful monitoring and optimal weight-based dosing nomograms, only 30% of patients are within the therapeutic range at 12 hours.[40] It cannot be known whether performance in nonstudy hospitals is this good, but surveys of other interventions suggest that therapeutic performance is generally not as good in widespread practice as in clinical trials.[41] This would suggest that any therapeutic or safety advantages of LMWHs shown in clinical trials would be greater in practice, because monitoring and dose adjustment are not needed.

Implications for Further Research

Are LMWH interchangeable? The meta-analyses cited in this review have, by necessity, treated the various LMWH

TABLE 6

STEPs for Comparison of LMWHs to UFH

Safety	**Equal or LMWHs better** Meta-analyses suggest that LMWHs are safer, with fewer episodes of major bleeding. Individual randomized controlled trials show them to be equal but none of the trials have adequate power to show differences of the magnitude expected. Heparin-induced thrombocytopenia occurs less often with LMWHs. Osteoporosis may occur less frequently with LMWHs.
Tolerablility	**LMWHs better** Treatment with LMWHs reduces phlebotomy, allows early hospital discharge or complete outpatient treatment. Symptomatic intolerance is rarely reported with either.
Effectiveness	**Equal or LMWHs better** Meta-analyses suggest that LMWHs are more effective in reducing venographic recurrence and mortality. There are trends toward reduction in symptomatic recurrent events as well. Individual RCTs show the agents to be equal but none of the trials have adequate power to show differences of the magnitude expected.
Price	**? (LMWHs probably more cost-effective)** Overall costs are less when LMWHs are used, but there may be specific cost shifts (between different payors or between different departments in a hospital) that make this question impossible to answer for every circumstance.

LMWH denotes low-molecular-weight heparin; UFH, unfractionated heparin.

preparations as interchangeable. Hirsch and Levine noted that meta-analysis may not be appropriate in this setting, in which distinct agents with different dosing and pharmacologic properties were used in the original trials.[42] The clinical effects of LMWH, however, have proved remarkably similar, and any differences between the preparations are likely to be clinically unimportant.[43] The only clear resolution of this question would come from a prospective trial comparing two separate LMWHs. Since these are highly effective against DVT, such a trial would be plagued by the same statistical problems of inadequate power that have troubled trials comparing LMWH and UFH. It is unlikely that such a trial will be performed.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Comparisons between therapeutic agents should be made on the basis of the STEPs format as shown in Table 6. The evidence presented shows that LMWHs compare favorably with UFH in the treatment of DVT. The magnitude of benefit that would come from converting from UFH to LMWH is only moderate, since UFH is an effective treatment. The absolute risk reductions for thromboembolic complications and major bleeding are in the 1% to 4% range. This would translate into a number needed to treat (NNT) of 27 to 71 patients to prevent one thromboembolic complication and 27 to 62 patients to prevent one episode of major bleeding. For comparison, the NNT to prevent one myocardial infarction or cardiovascular death with lipid-lowering therapy is 16 in the secondary prevention setting and 53 in the primary prevention setting.44

The economic impact of converting to routine use of LMWH in place of UFH is a more complicated issue. There is evidence that overall costs go down because of lower labor and laboratory costs, as well as fewer complications. The opportunity to treat some patients as outpatients and to release others from the hospital earlier are also advantages that may create large cost savings. At a more practical level, however, this may involve cost shifts between different payers and departmental budgets, so that the cost analysis must be specific to any particular situation.

How strong must the evidence be to change a medical treatment of choice? If UFH is the current standard treatment, and only clear and convincing evidence of improved patient-oriented outcomes (mortality or long-term post-thrombotic complications) can change the standard, then LMWHs have not yet met that test. If, however, both treatments must be judged equally in terms of efficacy, safety, convenience, and cost with the best available evidence on hand, then LMWHs are clearly superior to UFH in the treatment of DVT and should replace UFH as the treatment of choice.

REFERENCES

1. Mueller RL, Scheidt S. History of drugs for thrombotic disease. Circulation 1994; 89:432-49.
2. Samama MM, Desnoyers PC, Conard J, Bousser MG. Acute ischemic stroke and heparin treatments. Thromb Haemost 1997; 78:173-9.
3. Collins R, Peto R, Bargent C, Sleight P. Aspirin, heparin and fibrinolytic therapy in suspected acute myocardial infarction. N Engl J Med 1997; 336:847-60.
4. Green D, Hirsh J, Heit J, Prins M, Davidson B, Lensing A. Low molecular weight heparin: a critical analysis of clinical trials. Pharm Rev 1994; 46:89-109.
5. Clagett GP, Anderson FA, Heit J, Levine MN, Wheeler HB. Prevention of venous thromboemolism in Fourth ACCP consensus conference on antithrombotic therapy. Chest 1995; 108(4S):312-34.
6. Bergmann JF, Neuhart E. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. Thromb Haemost 1996; 76:529-34.

7. Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin in the prevention of thromboembolism in medical inpatients. Haemostasis 1996; 26:127-39.
8. Prins MH, Gelsema R, Sing A, van Heerde L, Den Ottolander G. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin in stroke patients. Haemostasis 1989; 19:245-50.
9. Geerts W, Jay R, Code K, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. New Engl J Med 1996; 335:701-7.
10. Edmondson R, Cohen A, Das S, Wagner M, Kakkar V.Low-molecular weight heparin versus aspirin and dipyridamole after femoropopliteal bypass grafting. Lancet 1994; 344:914-8.
11. Green D, Twardowski P, Wei R, Rademaker A. Fatal pulmonary embolism in spinal cord injury. Chest 1994; 105:853-5.
12. Karsch K, Preisack M, Baildon R, et al. Low molecular weight heparin (reviparin) in percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1996; 28:1437-43.
13. Cohen M, Demers C, Gurfinkel E, et al, for the ESSENCE study group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. N Engl J Med 1997; 337:447-452.
14. Day R, Wong K, Yu Y, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. N Engl J Med 1995; 333:1588-93.
15. Oxman A, Cook D, Guyatt G, for the Evidence-Based Medicine Working Group. Users' guide to the medical literature, VI: how to use an overview. JAMA 1994; 272:1367-71.
16. Hayward R, Wilson M, Tunis S, Bass E, Guyatt G, for the Evidence-Based Medicine Working Group. Users' guide to the medical literature, VIII: how to use clinical practice guidelines, A: are the recommendations valid? JAMA 1995; 274:570-1632.
17. Guyatt G, Sackett D, Cook D, for the Evidence-Based Medicine Working Group. Users' guide to the medical literature, II: how to use an article about therapy or prevention, A: are the results of the study valid? JAMA 1993; 270: 2598-601.
18. van den Belt A, Prins M, Lensing A. Low molecular weight heparins in the treatment of venous thromboembolism [protocol]. In: Fowkes F, Janzon L, Kleijnen J, Leng G, eds. Peripheral vascular diseases module of the Cochrane database of systematic reviews, [updated 02 June 1997]. The Cochrane Collaboration; Issue 4. Oxford: Update Software; 1997.
19. Leizorovicz A. Comparison of the efficacy and safety of low molecular weight heparins and unfractionated heparin in the initial treatment of deep venous thrombosis. An updated meta-analysis. Drugs 1996; 52 (suppl) 7:30-7.
20. Leizorovicz A, Simonneau G, Decousus H, Boissel J. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis. Brit Med J 1994; 309:299-304.
21. Hirsch J, Siragusa S, Cosmi B, Ginsberg J. Low molecular weight heparins in the treatment of patients with acute venous thromboembolism. Thromb Haemost 1995; 74:360-3.
22. Siragusa S. Cosmi B, Piovella F, Hirsch J, Ginsberg J. 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.
23. Lensing A, Prins M, Davidson B, Hirsh J. Treatment of deep venous thrombosis with low molecular weight heparins. A meta-analysis. Arch Intern Med 1995; 155:601-7.
24. Myers T, Hull R, Weg J. Fourth ACCP consensus conference on antithrombotic therapy: antithrombotic therapy for venous thromboembolic disease. Chest 1995; 4 (suppl):335s-51s.
25. Feissinger J, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. Thromb Haemost 1996; 76:195-9.
26. Luomanmaki K, Grankvist S, Hallert C, et al. A multicentre comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep vein thrombosis. J Intern Med 1996; 240:85-92.
27. The Columbus investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997; 337:657-62.
28. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE study group. N Engl J Med 1997; 337:663-9.
29. Levine M, Gent M, Hirsch 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.
30. Koopman M, 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. The Tasman study group. N Engl J Med 1996; 334:682-7.
31. Warkentin T, Levine M, Hirsch J, et al. Heparin-induced thrombocytopenia in patients treated with low molecular weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330-5.
32. Monreal M, Lafoz E, Olive A, del Rio L, Veida C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost 1994; 71:7-11.
33. Barbour L. Current concepts of anticoagulant therapy in pregnancy. Ob Gyn Clin N Am 1997; 24:499-512.
34. Weitz J. Low-molecular-weight heparins. New Engl J Med 1997; 337:688-98.
35. Hull R, Raskob G, Pineo G, et al. Treatment of proximal vein thrombosis with subcutaneous low-molecular-weight heparin vs intravenous heparin: an economic perspective. Arch Intern Med 1997; 157:289-94.
36. Drug Topics Redbook. Montvale, NJ: Medical Economics Co, 1997.
37. Crowther M, Hirsh J. Low-molecular-weight heparin for the out-of-hospital treatment of venous thrombosis: rationale and clinical results. Sem Throm Haemost 1997; 23:77-81.
38. Hirsh J, Fuster V. AHA medical/scientific statement special report. Guide to anticoagulant therapy. Part 1: Heparin. Circulation 1994; 89:1449-68.
39. Hull R, Raskob G, Brant R, Pineo G, Valentine K. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. Arch Intern Med 1997; 157:2562-8.
40. Schoenenberger R, Pearson S, Goldhaber S, Lee T. Variation in the management of deep vein thrombosis: implications for the potential impact of a critical pathway. Am J Med 1996; 100:278-282.
41. Stukenborg G. Comparison of carotid endarterectomy outcomes from randomized controlled trials and Medicare administrative databases. Arch Neurol 1997; 54:826-832.
42. Hirsch J, Levine M. Low molecular weight heparin. Blood 1992; 79:1-17.
43. Barrowcliffe T. Annotation: Low molecular weight heparins. Br J Haematol 1995; 90:1-7.
44. Rembold CM. Number-needed-to-treat analysis of the prevention of myocardial infarction and death by antidyslipidemic therapy. J Fam Pract 1996; 42:577-586.