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Low-Molecular-Weight Heparins Compared with Unfractionated Heparin for Treatment of Acute Deep Venous Thrombosis

A Cost-Effectiveness Analysis

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Background: Low-molecular-weight heparins are effective for treating venous thrombosis, but their cost-effectiveness has not been rigorously assessed.

Objective: To evaluate the cost-effectiveness of low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis.

Design: Decision model.

Data Sources: Probabilities for clinical outcomes were obtained from a meta-analysis of randomized trials. Cost estimates were derived from Medicare reimbursement and other sources.

Target Population: Two hypothetical cohorts of 60-year-old men with acute deep venous thrombosis.

Time Horizon: Patient lifetime.

Perspective: Societal.

Intervention: Fixed-dose low-molecular-weight heparin or adjusted-dose unfractionated heparin.

Outcome Measures: Costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios. An inpatient hospital setting was used for the base-case analysis. Secondary analyses examined outpatient treatment with low-molecular-weight heparin.

Results of Base-Case Analysis: Total costs for inpatient treatment were $26 516 for low-molecular-weight heparin and $26 361 for unfractionated heparin. The cost of initial care was higher in patients who received low-molecular-weight heparin, but this was partly offset by reduced costs for early complications. Low-molecular-weight heparin treatment increased quality-adjusted life expectancy by approximately 0.02 years. The incremental cost-effectiveness of inpatient low-molecular-weight heparin treatment was $7820 per QALY gained. Treatment with low-molecular-weight heparin was cost saving when as few as 8% of patients were treated at home.

Results of Sensitivity Analysis: When late complications were assumed to occur 25% less frequently in patients who received unfractionated heparin, the incremental cost-effectiveness ratio increased to almost $75 000 per QALY gained. When late complications were assumed to occur 25% less frequently in patients who received low-molecular-weight heparin, this treatment resulted in a net cost savings. Inpatient low-molecular-weight heparin treatment became cost saving when its pharmacy cost was reduced by 31% or more, when it reduced the yearly incidence of late complications by at least 7%, when as few as 8% of patients were treated entirely as outpatients, or when at least 13% of patients were eligible for early discharge.

Conclusions: Low-molecular-weight heparins are highly cost-effective for inpatient management of venous thrombosis. This treatment reduces costs when small numbers of patients are eligible for outpatient management.

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Low-molecular-weight heparin preparations are as safe and effective as unfractionated heparin for the treatment of acute deep venous thrombosis (1–4). These preparations have been shown to be cost-effective for thromboprophylaxis after hip replacement surgery compared with low-dose warfarin (5) or unfractionated heparin (6). We hypothesized that despite their current higher price, low-molecular-weight heparins might also be cost-effective relative to unfractionated heparin for treating established deep venous thrombosis. If therapy with low-molecular-weight heparin resulted in fewer bleeding complications or more effectively prevented thromboem-

See related article on pp 800-809 and editorial comment on pp 857-858.

bolic recurrences, the costs associated with these events would be reduced.

Substantial additional savings could be realized by avoiding or shortening hospitalization in selected patients who might be eligible for outpatient treatment with low-molecular-weight heparin. The feasibility of outpatient management of venous thrombosis was recently demonstrated in randomized trials (2–4). Up to 50% of participants in these trials received low-molecular-weight heparin at home. In an uncontrolled trial of dalteparin, 35% of participants were discharged within 24 hours of hospitalization and another 29% were discharged within 72 hours (7). In this study, low-molecular-weight heparin treatment resulted in large cost reductions compared with historical costs for inpatient care using unfractionated heparin.

We developed a decision model to compare the costs and health effects of low-molecular-weight heparins and unfractionated heparin for the treatment of acute deep venous thrombosis. In our base-case analysis, we assumed that all treatment occurred in an inpatient hospital setting. To fully quantify the potential economic impact of low-molecular-weight heparin treatment, we performed a secondary analysis that allowed for the possibility of outpatient treatment with this drug.

Methods

We performed a cost-effectiveness analysis by using a decision modeling approach (8–10). We adopted the recommendations of the Panel on Cost-Effectiveness in Health and Medicine for conducting and reporting a reference-case analysis (11). Accordingly, we assumed a societal perspective to produce results that would permit comparisons across different health care interventions (12). We expressed our results in terms of costs, life expectancy, quality-adjusted life expectancy, and incremental cost-effectiveness ratios.

Decision Model Structure and Assumptions

Figure 1 shows the structure of the decision model. The model specifies the clinical problem, treatment alternatives, early clinical outcomes, and late clinical outcomes.

Clinical Problem

The target population for this analysis was all adult patients with a confirmed diagnosis of acute, proximal, lower-extremity deep venous thrombosis. We compared treatment costs and clinical outcomes in two hypothetical cohorts of 10 000 patients with acute deep venous thrombosis. In each cohort, the representative patient was a 60-year-old, 75-kg man. We selected this patient because in randomized trials of low-molecular-weight heparin, slightly more than half of all participants were men, and in most of these trials, the mean age of participants was 57 to 64 years (2–4, 13–16).

Treatment Alternatives

Patients in the unfractionated heparin cohort received continuous intravenous infusion of unfractionated heparin by automatic pump at an average dosage of 30 000 U/d. Treatment was administered

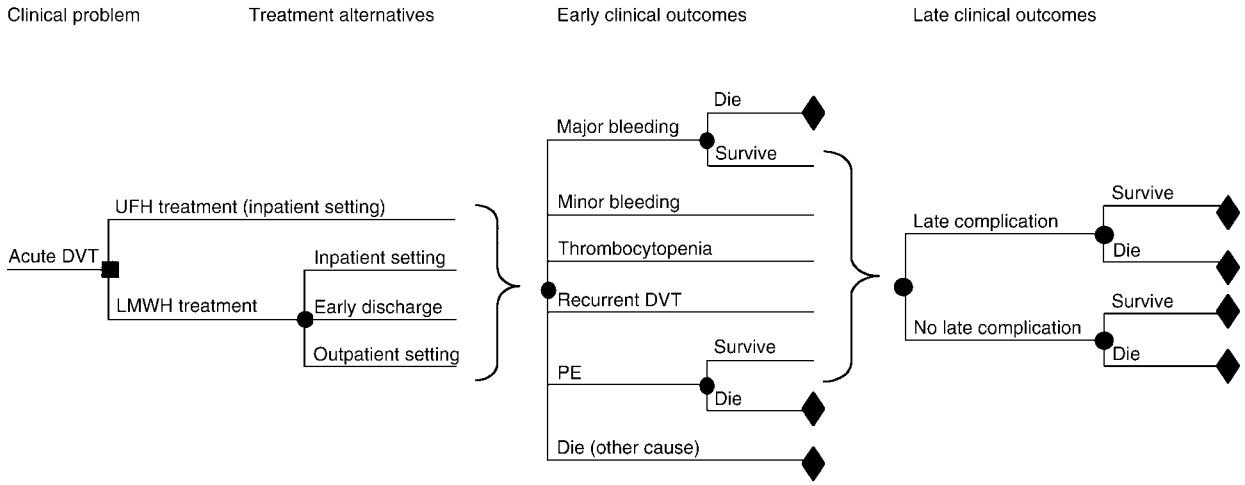

Figure 1. The cost-effectiveness decision model. At left, a square node represents the decision to treat acute deep venous thrombosis (*DVT*) with either unfractionated heparin (*UFH*) or low-molecular-weight heparin (*LMWH*). In the primary analysis, low-molecular-weight heparin treatment always occurred in an inpatient hospital setting. In the secondary analysis, some patients were eligible for early discharge or outpatient treatment, as indicated by the first round uncertainty node. All patients were at risk for early complications. Probabilities for early complications depended on the type of treatment received. Two early complications, major bleeding and pulmonary embolism (*PE*), were potentially fatal. All patients who did not develop a fatal early complication were at risk for a fatal or nonfatal late complication. Late complications included episodes of recurrent deep venous thrombosis and pulmonary embolism that occurred more than 6 months after the initial episode of deep venous thrombosis, mild and severe postphlebitic syndrome, superficial venous thrombosis, cellulitis, venous ulcer, varicose veins, stasis dermatitis, and deep venous insufficiency. The diamond-shaped nodes at the end of each path in the decision tree represent both the costs and the health effects associated with the full sequence of events in that particular path.

Table 1. Baseline Probabilities and Ranges for Clinical Outcomes

Outcome	Probability		Difference between Probabilities	Range Tested for Difference*	Reference
	Unfractionated Heparin Cohort	Low-Molecular-Weight Heparin Cohort			
	%		*percentage points*		
Early complications					
Minor bleeding	3.80	3.90	−0.10†	−1.63 to 1.42	17
Major bleeding	1.90	1.24	0.66	−0.09 to 1.41	17
Thrombocytopenia	1.80	1.19	0.61	−0.47 to 1.70	17
Recurrent deep venous thrombosis	4.40	3.04	1.36	−0.09 to 2.80	17
Pulmonary embolism	2.00	1.91	0.09	−0.83 to 1.01	17
Death	6.70	5.10	1.60	0.05 to 3.14	17
Late complications					
Mild postphlebitic syndrome					
After 1 year	14.70	14.70	0.00	−3.65 to 3.65	18
After 5 years	18.70	18.70	0.00	−4.65 to 4.65	18
Severe postphlebitic syndrome					
After 1 year	2.60	2.60	0.00	−0.65 to 0.65	18
After 5 years	9.30	9.30	0.00	−2.35 to 2.35	18

* Probability estimates and ranges tested for early complications were derived from meta-analysis results that were obtained by using a random-effects statistical model. Ranges for early complications were derived from the upper and lower 95% confidence limits for the difference between patients who received unfractionated heparin and those who received low-molecular-weight heparin.
† A negative difference favors unfractionated heparin treatment.

for a total of 6 days in a monitored inpatient setting. We assumed that the partial thromboplastin time was monitored on nine occasions in each of these patients and that necessary dose adjustments were made on the basis of this monitoring. Patients in the low-molecular-weight heparin cohort received fixed-dose enoxaparin, 1 mg/kg of body weight subcutaneously, twice daily for 6 days. We assumed that daily phlebotomy for complete blood counts was performed in both cohorts to monitor all hospitalized patients for covert bleeding and thrombocytopenia. We also assumed that oral anticoagulation with warfarin commenced during heparin treatment and continued for at least 3 months.

In the base-case analysis, we assumed that low-molecular-weight heparin treatment was always given in the inpatient setting. In the secondary analysis, we assumed that some patients treated with low-molecular-weight heparin could be discharged from the hospital early or could be treated entirely as outpatients.

Early Complications

We defined early complications as those that occurred during the initial heparin treatment period (fatal and nonfatal major bleeding, minor bleeding, and thrombocytopenia) or in the 6 months after the initial episode of deep venous thrombosis (recurrent deep venous thrombosis, fatal and nonfatal pulmonary embolism, or death from other causes). Each of these clinical outcomes was assumed to occur with a probability that depended on the choice of treatment but not on the treatment setting. Major and minor bleeding episodes that occurred during the period of oral anticoagulation were assumed to occur with equal frequencies in the two cohorts.

Late Complications

Late complications included episodes of recurrent deep venous thrombosis and pulmonary embolism that occurred more than 6 months after the initial episode of deep venous thrombosis, mild and severe postphlebitic syndrome, superficial venous thrombosis, cellulitis, venous ulcer, varicose veins, stasis dermatitis, and deep venous insufficiency.

Data and Assumptions

Probabilities for early and late complications, estimates of survival and quality-adjusted survival, and costs for initial treatment and subsequent care were derived from various clinical and administrative data sources.

Probabilities for Clinical Outcomes

Probabilities for early and late complications are summarized in **Table 1**. Probabilities for early complications were derived from a meta-analysis of randomized trials that compared a low-molecular-weight heparin preparation with unfractionated heparin for treatment of acute deep venous thrombosis (17). The meta-analysis identified 11 eligible studies (1–4, 13–16, 19–21). Clinical outcomes included major and minor bleeding complications and thrombocytopenia during the initial heparin treatment period and recurrent deep venous thrombosis, pulmonary embolism, and mortality in the 6 months after the initial episode of deep venous thrombosis. Because several studies enrolled some patients with calf venous thrombosis (4, 14–16, 21) and because the natural history of calf venous thrombosis differs from that of proximal thrombosis (22, 23), probability estimates for recurrent deep venous thrombosis, pulmonary embolism, and death were derived

Table 2. Estimates for Quality-of-Life Adjustments

Variable	Estimate	Range Tested	Reference	Notes
Age- and sex-specific utilities*				
Men 63 to 64 years of age	0.87	0.84–0.91	27	Mean time-tradeoff utility (range = 95% CI) for community sample (n = 160)
Men 65 to 84 years of age	0.84	0.80–0.88	27	Mean time-tradeoff utility (range = 95% CI) for community sample (n = 147)
Men 85 years of age or older	0.82	0.57–1.00	27	Mean time-tradeoff utility (range = 95% CI) for community sample (n = 6)
Utilities for late complications*				
Mild postphlebitic syndrome	1.00	0.91–1.00	28	Median standard-gamble utility (range = 95% CI) for healthy volunteers (n = 30)
Severe postphlebitic syndrome	0.93	0.79–1.00	28	Median standard-gamble utility (range = 95% CI) for healthy volunteers (n = 30)
Decrements in utility for early complications, d*				
Minor bleeding	1	0–2		Assumes 1 additional day of hospitalization
Major bleeding	5	4–6	29	Mean length of stay for gastrointestinal hemorrhage at short-term, general, nonfederal hospitals in 1995–1996 (n = 31 070)
Thrombocytopenia	1	0–2		Assumes 1 additional day of hospitalization
Recurrent deep venous thrombosis	6	4–8	29	Mean length of stay for deep venous phlebitis of the leg at short-term, general, nonfederal hospitals in 1995–1996 (n = 5033)
Pulmonary embolism	8	6–10	29	Mean length of stay for pulmonary embolism at short-term, general, nonfederal hospitals in 1995–1996 (n = 16 185)

* Age- and sex-specific utilities are expressed as a proportion of the value of full health; utilities for late clinical outcomes are expressed as a proportion of the age- and sex-specific value. Decrements in utility for early clinical outcomes are expressed as days lost from quality-adjusted life expectancy because of hospitalization.

from a subgroup analysis restricted to patients with proximal thrombosis. We used meta-analysis results that were obtained with a random-effects statistical model because this model produced wider CIs than the fixed-effects model.

We used data from an observational study of the long-term course of acute deep venous thrombosis to estimate incidence rates for mild and severe postphlebitic syndrome (18). We assumed that incidence rates for these complications were equal for the two treatment cohorts, because this study did not compare rates in patients who received low-molecular-weight heparin and those who received unfractionated heparin.

Estimation of Life Expectancy

We constructed survival curves to model the life span of patients in each cohort from the time of the initial episode of venous thrombosis to death. We used mortality data from the previously described meta-analysis to estimate survival during the first 6 months after deep venous thrombosis. Survival during the next 18 months was based on a single randomized trial of low-molecular-weight heparin treatment in which patients were followed for 2 years (24). We assumed that survival was identical for the two cohorts after this time. Survival for the period 3 to 15 years after deep venous thrombosis was based on an observational study of long-term complications and survival after acute deep venous thrombosis (25). To complete survival curves up to 99 years of age, we used data from the 1994 U.S. Life Table for men (26).

Quality-of-Life Adjustments

We adjusted life expectancy for quality of life by using health state utilities (**Table 2**). Utilities represent an individual patient's preference for a given health state and are scaled from 0 to 1 (30, 31). Quality-adjusted life-years (QALYs) are calculated by multiplying the time spent in a given health state by the utility value for that health state. For the health state associated with no complication after acute deep venous thrombosis, we used age- and sex-specific time-tradeoff utilities obtained from a community sample of adults (27). Quality weights for mild and severe postphlebitic syndrome were based on standard gamble utilities obtained from healthy volunteers (28). We assumed that patients who received low-molecular-weight heparin and those who received unfractionated heparin had the same utility for the health state associated with the initial episode of deep venous thrombosis, regardless of whether low-molecular-weight heparin was given in the hospital or outpatient setting. Decrements in utility for recurrent thromboembolic events and treatment complications were expressed in days lost because of hospitalization (29).

Cost of Initial Treatment

To calculate the cost of inpatient treatment with heparin, we added costs for hospital care, physician services, and 6 days of treatment with either low-molecular-weight heparin or unfractionated heparin. Hospital costs were based on average Medicare reimbursement for deep venous thrombophlebitis in 1995 (32) minus the estimated pharmacy and supply

costs for treatment with unfractionated heparin. Costs for physician services were based on 1996 Medicare reimbursement rates for an initial hospital visit and for subsequent care on each hospital day (33). Pharmacy costs for unfractionated heparin and low-molecular-weight heparin (enoxaparin) were $9.94 per 25 000 U ($12 per day) and $16.80 per 30 mg ($84 per day), respectively, based on reported average wholesale prices (34). We assumed that supplies and ancillary resources needed for unfractionated heparin treatment included an intravenous catheter and tubing, an automatic pump, and phlebotomy with monitoring of partial thromboplastin time on nine occasions. For patients who received low-molecular-weight heparin, supplies and ancillary resources included syringes and needles and daily phlebotomy during hospitalization. Costs for supplies and ancillary resources were derived from a proprietary cost accounting system by using only the variable cost component (Transition I, Transition Systems, Inc., Boston, Massachusetts). The assigned values for these and other cost estimates are outlined in **Table 3**. We did not include time costs associated with administering heparin or making dose adjustments. Not including these costs potentially biased our results in favor of unfractionated heparin. Total costs for the initial hospital treatment of deep venous thrombosis with low-molecular-weight heparin and unfractionated heparin were $3638 and $3402, respectively. All costs were converted to 1997 U.S. dollars by using the gross domestic product deflator.

For the secondary analysis, assumptions about outpatient resource utilization and the proportion of patients eligible for outpatient management were based on data from two randomized trials that enrolled patients without regard to their eligibility for outpatient treatment (2, 4). We assumed that 30% of patients who received low-molecular-weight heparin were treated entirely as outpatients and that another 25% were discharged after approximately 3 days. We also assumed that 15% of outpatients required a daily visit from a home health aide and that outpatients averaged 3.6 physician office visits and four telephone calls for every 6 outpatient days (2). Assigned costs for home health care and outpatient office visits were based on Medicare reimbursement rates (33, 35). Time costs for answering telephone calls were based on median weekly earnings for registered nurses in 1997 (36). Patient transportation costs were assumed to be $15 per outpatient visit. We assumed that family members would provide home care for 4 hours each day, and assigned costs for this care were based on average, seasonally adjusted earnings for non–farm production workers in 1997 (36). Persons who were treated entirely as outpatients were assumed to undergo initial evaluation in the emergency department, including duplex sonography of the affected lower extremity. For this evaluation, costs for professional services were based on Medicare reimbursement, and costs for emergency and radiology services were derived from the Transition I cost accounting system.

Cost of Early Complications

We assumed that minor bleeding complications and thrombocytopenia each resulted in 1 additional day of hospitalization and 1 additional day of physician services for subsequent hospital care. Because randomized trials have shown that more than half of all thromboembolic recurrences after acute deep venous thrombosis occur after the initial treatment period (1, 2, 4), we assumed that recurrent deep venous thrombosis and pulmonary embolism would lead to readmission for a full hospital stay. Assigned costs for these complications were based on average Medicare reimbursement for deep venous thrombophlebitis and pulmonary embolism (32). By definition, major bleeding always occurred during the initial treatment period. We assumed that major bleeding complications were uniformly distributed over this period and that hospital length of stay increased from 0 days if bleeding occurred on the first hospital day to 5 days if bleeding occurred on the sixth hospital day. Therefore, major bleeding resulted in an average additional length of stay of 2.5 days. We assumed that outpatients who developed major bleeding incurred costs for a full hospitalization for gastrointestinal hemorrhage (32).

Cost of Late Complications

Costs for late complications were derived from an observational study of long-term complications of deep venous thrombosis in a cohort of 257 Swedish patients, most of whom were probably treated with unfractionated heparin (25). In this study, the average cost of the initial episode of deep venous thrombosis was based on reported unit prices and was approximately two times greater than our estimate based on Medicare reimbursement. To correct for this discrepancy, we recalculated reported yearly per-patient costs for long-term complications after adjusting for this factor. We assumed that per-patient costs were equal for patients who received low-molecular-weight heparin and those who received unfractionated heparin, but we included these costs because more patients receiving low-molecular-weight heparin were at risk for complications during the first 2 years of follow-up.

Future Health Care Costs

Costs of future health care were also included because slightly more patients receiving low-molecular-weight heparin were alive during the first 2 years of

Table 3. Cost Estimates*

Variable	Estimate	Range Tested†	Source or Reference	Notes
Costs for initial inpatient treatment, *$*				
6-day hospitalization, excluding pharmacy and supplies	2796	2100–3500	32	Average Medicare reimbursement for DRG 128 (deep venous thrombophlebitis) based on 20 654 discharges; minus estimated costs for pharmacy, supplies, and ancillary resources for unfractionated heparin treatment
Physician services	271	200–340	33	Medicare reimbursement rate of $34.63 per RVU for initial physician visit (CPT code 99222 = 2.97 RVUs) plus 0.92 RVUs for each of five subsequent visits (CPT code 99231)
Unfractionated heparin				
Daily pharmacy costs	12	9–15	34	Average wholesale price, $9.94 per 25 000 U; average dosage, 30 000 U/d
Daily supplies and ancillary resources	44	33–55	TSI	Includes intravenous catheter ($3.65) and tubing ($1.20), automatic pump ($3.89 per day), phlebotomy ($9.62), and partial thromboplastin time monitoring ($15.23) on nine occasions over 6 days
Low-molecular-weight heparin				
Daily pharmacy costs	84	63–105	34	Average wholesale price, $16.80 per 30 mg; dosage, 1 mg/kg of body weight (75 mg) twice daily
Daily supplies and ancillary resources	11	8–14	TSI	Includes daily phlebotomy ($9.62 per day) while hospitalized and syringes and needles ($1 per day)
Costs for outpatient resources, *$*‡				
Emergency department evaluation	379	285–475	TSI, 33	Includes $140 for level 4 emergency care (TSI variable cost component), plus $68 for duplex sonography (TSI variable cost component), plus Medicare reimbursement rate of $34.63 per RVU for interpretation (CPT code 76880 = 2.34 RVUs), plus 2.44 RVUs at $35.42 per RVU for evaluation and management services (CPT code 99284)
Physician office visits per outpatient day	21	15–25	2, 33	Medicare reimbursement rate of $35.42 per RVU for office visit (CPT code 99213 = 0.96 RVUs) plus transportation cost of $15 per outpatient visit; 0.60 visits per outpatient day
Telephone calls to physician's office per outpatient day	3	2–4	2, 36	Median weekly earnings for registered nurses in 1994 were $682; 0.65 calls per outpatient day; assume 15 minutes per call
Home care by visiting aid per outpatient day	10	8–13	2, 35	Projected Medicare reimbursement rate of $68 per visit; 1 visit per day for 15% of outpatients
Home care by family member per outpatient day	49	37–61	36	Average, seasonally adjusted earnings for production workers in March 1997; assumes 4 hours per day at $12.19 per hour
Miscellaneous, %				
Patients in low-molecular-weight heparin cohort eligible for outpatient treatment	30	25–35	2, 4	Range derived from percentage of patients eligible for outpatient treatment in two randomized trials
Patients in low-molecular-weight heparin cohort eligible for early discharge	25	15–40	2, 4	Range derived from percentage of patients eligible for early discharge in two randomized trials
Discount rate	3	0–5		
Costs of early complications, *$*				
Minor bleeding	499	375–625	32, 33	Assume 1 additional hospital day ($466) plus one additional physician visit at $34.63 per RVU (CPT code 99231 = 0.92 RVUs)
Major bleeding				
Inpatients	1245	934–1556	32, 33	Assume 2.5 additional hospital days ($1165) plus 2.5 additional physician visits at $34.63 per RVU (CPT 99231 code = 0.92 RVUs)
Outpatients‡	4149	3110–5190	32, 33	Average Medicare reimbursement for DRG 174 (gastrointestinal hemorrhage) based on 246 607 discharges plus Medicare reimbursement rate of $34.63 per RVU for initial physician visit (CPT code 99222 = 2.97 RVUs), plus 0.92 RVUs for each of four subsequent physician visits (CPT code 99231), plus 4.88 RVUs for upper endoscopy (CPT code 43234)
Thrombocytopenia	499	375–625	32, 33	Assume 1 additional hospital day ($2796/6) plus 1 additional physician visit at 34.63 RVUs (CPT code 99231 = 0.92 RVUs)
Recurrent deep venous thrombosis	3485	2610–4360	32, 33	Average Medicare reimbursement for DRG 128 (deep venous thrombophlebitis) based on 20 654 discharges, plus Medicare reimbursement rate of $34.63 per RVU for initial physician visit (CPT code 99222 = 2.97 RVUs), plus 0.92 RVUs for each of five subsequent physician visits (CPT code 99231), plus 2.34 RVUs for interpretation of duplex sonogram (CPT code 76880)
Pulmonary embolism	6187	4640–7730	32, 33	Average Medicare reimbursement for DRG 078 (pulmonary embolism) based on 30 638 discharges; plus Medicare reimbursement rate of $34.63 per RVU for initial physician visit (CPT code 99222 = 2.97 RVUs), plus 0.92 RVUs for each of seven subsequent physician visits (CPT code 99231), plus 7.35 RVUs for interpretation of perfusion lung scan (CPT code 78584)
Death from any cause	5000	3750–6520		Most early deaths are not due to major bleeding or pulmonary embolism; such deaths incurred costs for both complications and death
Lifetime cost of late complications			25	Adjusted costs for late complications up to 15 years after the initial episode of deep venous thrombosis
Unfractionated heparin cohort	2346			
Low-molecular-weight heparin cohort	2368	1776–2960		
Future (unrelated) health care costs			37	Average, annual, age-specific health care expenditures minus costs for late complications, summed over entire patient life span
Unfractionated heparin cohort	19 949			
Low-molecular-weight heparin cohort	19 990	19 949–19 990		Range tested reflects impact of including or not including future health care costs

* CPT = Current Procedural Terminology; DRG = diagnosis-related group; RVU = relative value unit; TSI = Transition I cost accounting system (Transition Systems, Inc., Boston, Massachusetts).
† Ranges were derived by adding or subtracting 25% to or from the baseline estimate, except where otherwise noted.
‡ These costs were relevant to the secondary analysis.

follow-up, although the annual costs for each group were again assumed to be equal on a per-patient-at-risk basis. Our estimate for these costs was based on age-specific, average, annual health care expenditures in 1995 (37). These costs were adjusted by subtracting yearly per-patient costs for long-term complications of deep venous thrombosis.

Time Preference

To reflect individual patient preferences for having material goods sooner rather than later, we discounted all costs and health effects at an annual rate of 3% (9). Discount rates between 0% and 5% were tested in the sensitivity analysis.

Calculation of Incremental Cost-Effectiveness Ratios

For each treatment strategy, we calculated the expected value of total costs by multiplying the probability of each unique outcome with its associated costs and then adding these values for all possible outcomes. Life expectancy for each cohort was determined by calculating the area under the survival curves. Quality-adjusted life expectancy was calculated by multiplying the yearly probability of survival by its corresponding quality weight and summing these values over the entire life span. We then calculated the incremental cost-effectiveness of low-molecular-weight heparin relative to unfractionated heparin by dividing the difference in costs by the difference in life expectancy (or quality-adjusted life expectancy). For example, if low-molecular-weight heparin treatment was associated with a total cost of $20 000 and a life expectancy of 10 QALYs and unfractionated heparin was associated with a total cost of $18 000 and a life expectancy of 9.5 QALYs, the incremental cost-effectiveness of treatment with low-molecular-weight heparin would be $4000 per QALY gained ([$20 000 − $18 000]/[10 − 9.5] = $2000/0.5 = $4000).

Sensitivity Analysis

We used sensitivity analysis to identify important model uncertainties. When possible, ranges for variables were based on reported or calculated 95% CIs from the data sources. Otherwise, we determined ranges by adding or subtracting 25% from the baseline estimate.

Results

Base-Case Analysis

Average total costs associated with inpatient treatment with low-molecular-weight heparin were $26 516, whereas costs associated with unfractionated heparin treatment were $26 361, resulting in a net difference of $155 per patient treated. Treatment with low-molecular-weight heparin resulted in 9.43 life-years or 8.00 QALYs, and treatment with unfractionated heparin resulted in 9.41 life-years or 7.98 QALYs. Thus, treatment with low-molecular-weight heparin resulted in a net gain of 0.02 life-years (or 0.02 QALYs). This corresponds to an increase in life expectancy of approximately 8 days. The incremental cost-effectiveness of low-molecular-weight heparin was calculated to be $6910 per life-year gained or $7820 per QALY gained. When compared with cost-effectiveness ratios for other widely accepted medical interventions, inpatient treatment of acute deep venous thrombosis with

Table 4. Results of the Cost-Effectiveness Analysis*

Variable	Low-Molecular-Weight Heparin Cohort	Unfractionated Heparin Cohort	Difference
Base-case analysis			
Initial treatment costs, *$*	3638	3402	236
Early complication costs, *$*	520	664	−144
Late complication costs, *$*	2368	2346	22
Future health care costs, *$*	19 990	19 949	41
Total costs, *$*	26 516	26 361	155
Life expectancy, *y*	9.429	9.406	0.022
Quality-adjusted life expectancy, *QALYs*	7.998	7.978	0.020
Incremental cost-effectiveness, *$/life-year*	–	–	6910
Incremental cost-effectiveness, *$/QALY* gained	–	–	7820
Secondary analysis†			
Initial treatment costs, *$*	2701	3402	−701
Early complication costs, *$*	540	664	−124
Late complication costs, *$*	2368	2346	22
Future health care costs, *$*	19 990	19 949	41
Total costs, *$*	25 599	26 361	−762
Life expectancy, *y*	9.429	9.406	0.022
Quality-adjusted life expectancy, *QALYs*	7.998	7.978	0.020
Incremental cost-effectiveness, *$/life-year*	–	–	Low-molecular-weight heparin dominant
Incremental cost-effectiveness, *$/QALY* gained	–	–	Low-molecular-weight heparin dominant

* QALY = quality-adjusted life-year.
† In the secondary analysis, 30% of patients receiving low-molecular-weight heparin received outpatient treatment, and 25% were discharged from the hospital after 3 days.

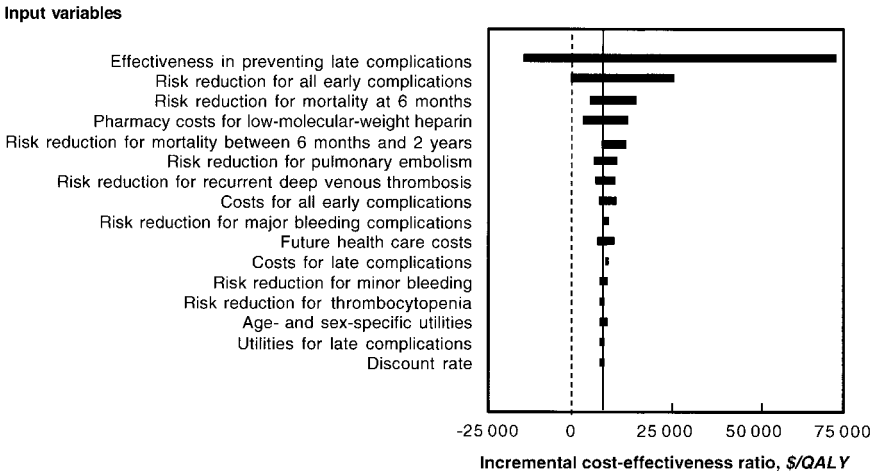

Figure 2. Tornado diagram showing the results of univariate sensitivity analyses. The solid vertical line represents the incremental cost-effectiveness of inpatient treatment with low-molecular-weight heparin relative to treatment with unfractionated heparin when all variables were set at their baseline value. Horizontal bars indicate the range in incremental cost-effectiveness ratios obtained by setting each variable at the lower and upper limit of its range and holding all other variables constant at their baseline value. Incremental cost-effectiveness ratios less than $0 (*dashed vertical line*) indicate that treatment with low-molecular-weight heparin is cost saving. The cost-effectiveness of inpatient treatment with low-molecular-weight heparin was sensitive to only one variable: the effectiveness in preventing late complications. When other model variables were tested over a wide range of values, the cost-effectiveness ratio for inpatient treatment with low-molecular-weight heparin was always less than $25 000 per quality-adjusted life-year (*QALY*) gained.

low-molecular-weight heparin seems to be highly cost-effective (38).

Disaggregated costs for patients who received low-molecular-weight heparin included $3638 for initial treatment, $520 for early complications, $2368 for late complications, and $19 990 for future health care. For patients who received unfractionated heparin, disaggregated costs included $3402 for initial treatment, $664 for early complications, $2346 for late complications, and $19 949 for future health care. These results are summarized in the upper portion of **Table 4**.

Secondary Analysis

Results of the secondary analysis are shown in the lower portion of **Table 4**. For this analysis, we assumed that 30% of patients in the low-molecular-weight heparin cohort were treated entirely as outpatients and that another 25% were discharged early after a 3-day hospital stay. Life expectancy, quality-adjusted life expectancy, and costs for late complications and future health care were unchanged from the base-case analysis. However, initial treatment costs were only $2701 per patient in the low-molecular-weight heparin cohort compared with $3402 per patient in the unfractionated heparin cohort. Costs of early complications increased to $540 in the low-molecular-weight heparin group. Treatment with low-molecular-weight was found to be a dominant alternative because it resulted in greater quality-adjusted life expectancy and reduced average costs by $760 per patient treated.

When we modified our assumptions so that 100% of the low-molecular-weight heparin cohort received outpatient treatment, initial treatment costs were reduced to $1560 and total cost savings amounted to almost $1900 per patient.

Sensitivity Analysis

As illustrated in **Figure 2**, the cost-effectiveness of low-molecular-weight heparin was sensitive to our baseline assumption that late complications occurred with equal frequency in the two treatment cohorts. When these complications were assumed to occur 25% less frequently in patients who received unfractionated heparin, the incremental cost-effectiveness ratio increased to almost $75 000 per QALY gained. Conversely, when we assumed that these complications occurred 25% less frequently in patients who received low-molecular-weight heparin, the latter treatment resulted in a net cost savings. When we tested other model variables over a wide range of values, the cost-effectiveness ratio for inpatient treatment with low-molecular-weight heparin was always less than $25 000 per QALY gained.

We performed threshold analyses to determine under what conditions low-molecular-weight heparin treatment was cost saving. Inpatient treatment with low-molecular-weight heparin became less costly when its pharmacy cost was reduced by 31% or more (from $84 per day to less than $58 per day). Inpatient treatment with low-molecular-weight heparin also provided cost savings when it reduced the yearly incidence of late complications by at least 7%. Finally, treatment with low-molecular-weight heparin became less expensive when as few as 8% of patients were treated entirely as outpatients or when at least 13% were eligible for early discharge.

Figure 3 illustrates the results of a sensitivity analysis that varied three model variables: pharmacy costs for low-molecular-weight heparin, treatment costs for early complications, and the effectiveness of low-molecular-weight heparins in preventing early complications. Because probabilities and costs

for early complications represented bundled values for multiple different complications, these three variables encompassed most of the variables in the model and allowed us to examine the combined influence of as many potentially important variables as possible. Although we widely varied our baseline estimates, the cost-effectiveness ratio for inpatient treatment with low-molecular-weight heparin was almost always less than $25 000 per QALY except when it was assumed to be at the lower limit of effectiveness in preventing early complications and when the pharmacy cost was $105 per day or more.

Discussion

We have shown that treatment with low-molecular-weight heparin is highly cost-effective for inpatient management of acute, proximal deep venous thrombosis relative to conventional treatment with unfractionated heparin. The incremental cost-effectiveness ratio of $7820 per QALY gained represents a small additional cost of $155 per patient treated and a corresponding small increase of approximately 0.02 QALYs. Although the initial treatment costs were greater for patients in the low-molecular-weight heparin cohort, these were partly offset by reduced costs for treating early complications.

When we considered the possibility of outpatient management, we found that low-molecular-weight heparins provided substantial cost savings under a series of reasonable assumptions about patient eligibility and resource utilization. When just more than half of all patients were eligible for partial or complete outpatient management, treatment with low-molecular-weight heparin saved an average of $790 per patient treated. Our threshold analysis revealed that low-molecular-weight heparin treatment achieved dominance when as few as 8% of patients were treated as outpatients or when at least 13% were discharged after 3 days of hospitalization.

Sensitivity testing demonstrated that our conclusions about effectiveness were robust over a wide range of values for almost all important model uncertainties. One exception to this involved the relative effectiveness of low-molecular-weight heparin in preventing late complications. When we assumed that unfractionated heparin was 25% more effective than low-molecular-weight heparin for preventing late complications, the cost-effectiveness ratio approached $75 000 per QALY. However, we believe it is more likely that late complications would occur either with equal or lower frequency in patients receiving low-molecular-weight heparin; two studies have demonstrated superior thrombus resolution after treatment with low-molecular-weight heparin (13, 19), whereas other studies have shown no difference between treatments in the degree of venographic improvement (14–16, 21).

Our conclusions complement and extend the findings of other investigators. In an observational study of the feasibility of outpatient treatment with dalteparin, 35% of patients were discharged within 24 hours and more than half were discharged within 3 days (7). Total treatment costs were reduced by almost 35% compared with costs for historical controls who had received unfractionated heparin in the inpatient setting. The findings of this study are limited by its use of historical controls and incompletely described methods for calculating costs. We found that costs for initial treatment and early complications were reduced by almost 25% when outpatient treatment with low-molecular-weight heparin was possible.

Hull and colleagues (39) performed an economic analysis by using data from a single multicenter randomized trial. These investigators reported that inpatient treatment with tinzaparin was less costly than treatment with unfractionated heparin and calculated a net savings of approximately $40 per patient treated. This analysis differed from ours in several respects. First, we assumed a societal perspective, whereas Hull and colleagues adopted the perspective of a third-party payer. Second, we pooled data from multiple sources, whereas these authors collected data on effectiveness and costs from collaborating centers. Third, because we used a modeling approach, we were able to extend the time horizon of our analysis to cover the entire life

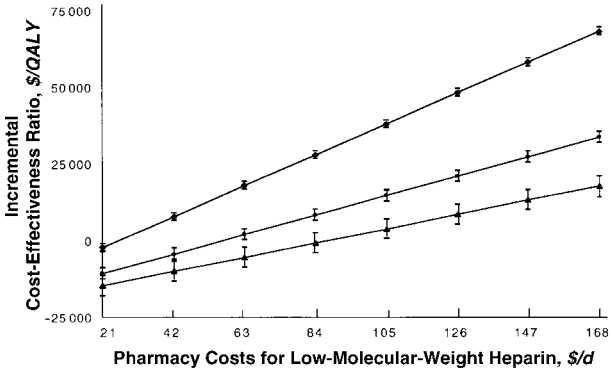

Figure 3. Results of multivariate sensitivity analysis. Each solid line indicates the incremental cost-effectiveness of inpatient treatment with low-molecular-weight heparin relative to unfractionated heparin at various levels of pharmacy costs for low-molecular-weight heparin. The middle line (*circles*) represents baseline assumptions about the effectiveness of low-molecular-weight heparin in preventing early complications. The upper (*diamonds*) and lower (*triangles*) lines represent the incremental cost-effectiveness of low-molecular-weight heparin treatment at its lower and upper limits of effectiveness in preventing early complications. Vertical bars represent the effect of varying the cost of treating early complications by ±25%. A negative cost-effectiveness ratio indicates that low-molecular-weight heparin is a cost-saving strategy. The cost-effectiveness ratio for inpatient treatment with low-molecular-weight heparin was almost always less than $25 000 per quality-adjusted life-year (*QALY*) except when low-molecular-weight heparin was assumed to be at the lower limit of effectiveness in preventing early complications and the pharmacy cost was $105 (125% of the baseline estimate) or greater.

span of each patient, whereas their time horizon was necessarily restricted to the duration of the trial. Finally, our assigned pharmacy costs for low-molecular-weight heparin, which were based on the average wholesale price, were much higher than Hull and colleagues' hospital-derived costs. Our use of average wholesale prices was appropriate for the societal perspective of this analysis because they closely approximate true opportunity costs (40).

Our study has several limitations. Our probability estimates for early complications were based on studies that evaluated multiple, different low-molecular-weight heparin preparations. Because these preparations differ in their molecular weight, anti-factor Xa activity, and degree of protein binding, they may differ with respect to their safety and effectiveness (41). By using results from multiple studies, we implicitly assumed that all preparations were equally safe and effective. Little evidence exists to support or refute this assumption. Of the five low-molecular-weight heparin preparations that have been studied for treating venous thrombosis, two are available for use in the United States: enoxaparin and dalteparin. We based our pharmacy costs on the average wholesale price of enoxaparin. Of note, the average wholesale price for dalteparin is less than that for enoxaparin but is not less than the cost-saving threshold of $58 per day.

An additional limitation involves our assumption that clinical effectiveness was independent of the treatment setting. Those who received outpatient treatment with low-molecular-weight heparin had the same risk for bleeding complications and recurrences as those who were treated as inpatients. This assumption has not been confirmed in clinical trials. In fact, meta-analysis results suggest that low-molecular-weight heparins may have been more effective in preventing major bleeding complications in inpatient treatment studies compared with studies in which outpatient treatment was possible (17). However, these studies did not report bleeding outcomes separately for inpatients and outpatients; thus, reliable estimates of bleeding complications in outpatients are not available.

Some assumptions potentially bias our analysis in favor of unfractionated heparin. Low-molecular-weight heparin treatment would have been more strongly favored if we had considered nursing time costs for drug administration or if we had not assumed that inpatient and outpatient treatment had the same utility.

We conclude that low-molecular-weight heparins are highly cost-effective relative to unfractionated heparin for inpatient treatment of acute deep venous thrombosis. Outpatient treatment with low-molecular-weight heparin holds potential for substantial cost savings. Although decisions about resource utilization are always subject to budgetary constraints, it would be reasonable to treat hospitalized patients with low-molecular-weight heparin. Outpatient treatment with low-molecular-weight heparin in eligible patients not only is beneficial from the societal perspective but also is likely to be a highly attractive option for many individual patients.

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