Comparing the Costs, Risks, and Benefits of Competing Strategies for the Primary Prevention of Venous Thromboembolism

Jerry Avorn, MD; Wolfgang C. Winkelmayer, MD, ScD

Abstract—Systematic cost-effectiveness analyses of regimens used for preventing venous thromboembolism (VTE) are becoming increasingly important for several reasons: the aging of the population, with an accompanying increase in admissions for orthopedic procedures or other surgery; expanded indications for thromboprophylaxis in nonsurgical patients; and the introduction of more expensive new agents that may increase safety and efficacy. At the same time, health care systems are under unprecedented pressure to contain the costs of care, particularly medications. Such economic analyses are made more difficult by the paucity of clinical trials comparing treatment regimens to one another rather than to placebo. Several methodological issues must be kept in mind when evaluating cost-effectiveness analyses of VTE prophylaxis. These include the perspective from which the analysis is performed (eg, the health care system as a whole versus a particular payer), limitations of trial data (eg, artificially short time horizons), and definition of outcomes (eg, flawed definition and grouping together of adverse effects or treatment failures). Quantifying costs across nations and health care systems is problematic as well. Another challenge is the extrapolation of efficacy data from highly monitored study patients to routine practice settings. Nevertheless, cost-effectiveness analyses of VTE treatments conducted in orthopedic surgery, trauma, general surgery, and acute medical settings can help define the relationships among expenditures, adverse outcomes, and patient benefit for particular therapeutic strategies in a variety of clinical situations. (Circulation. 2004;110[suppl IV]:IV-25–IV-32.)

Key Words: venous thromboembolism ■ cost-effectiveness ■ prophylaxis ■ low-molecular-weight heparin ■ low-dose unfractionated heparin ■ warfarin

In recent years, several factors have emerged that increase the importance of economic assessment of regimens used for the primary prevention of venous thromboembolism (VTE). For many decades, unfractionated heparin (UFH) and warfarin were the mainstays of treatment in this clinical setting. However, beginning in the 1990s and continuing to the present, new agents appeared that held the promise of greater efficacy and/or safety, albeit at greater financial cost. Moreover, new clinical and epidemiologic information emerged that stressed the importance of prophylaxis for VTE in a growing number of common clinical situations. These developments have occurred at the same time that health care systems throughout the world face unprecedented pressures to contain the costs of care. This has been particularly true for medications, which represent the fastest growing component of health care costs, rising between 13% and 19% annually in recent years.

Measuring the cost-effectiveness of medical interventions is a relatively new field; its methodologies are still evolving and are, on occasion, controversial. Nevertheless, consensus has developed over the appropriate broad approach to this discipline: given that an adequate evidence base of data from clinical studies and other sources is available, established tools should be used to compare the outcomes of a medication (both positive and negative) with the costs of its use. Sufficient information from controlled clinical trials is vital in laying the foundation for such analyses. When clinical trials have randomly allocated patients to several active treatment arms (eg, a low-molecular-weight heparin [LMWH] versus UFH), their data can serve as the input to cost-effectiveness analyses. The fact that some form of VTE prophylaxis is increasingly considered the appropriate standard of care has helped further such analyses, in that studies comparing active treatment with placebo have become less common. However, this is not the case in all clinical settings, and some key recent trials still allocated patients to active treatment versus placebo. Although this is useful for establishing a minimum definition of efficacy, in the absence of head-to-head studies comparing competing regimens, cost-effectiveness analyses must attempt to simulate “virtual” comparative studies by stringing together several trials of active drug compared with placebo, a much less satisfactory analytic approach.
TABLE 1. Methodological Considerations in Cost-Effectiveness Analyses

<table>
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<tr>
<th>Factor</th>
<th>Consideration</th>
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<tr>
<td>Perspective taken</td>
<td>Societal (recommended), payer, hospital, service, patient</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Within-hospitalization, entire episode, or lifetime</td>
</tr>
<tr>
<td>Setting</td>
<td>Tertiary care vs routine care; cross-national differences</td>
</tr>
<tr>
<td>Discounting</td>
<td>For both costs and effects, 3% per year recommended</td>
</tr>
<tr>
<td>Outcome definition</td>
<td>Failure of prophylaxis can be severe (eg, PE) or minor (eg, asymptomatic distal thrombophlebitis); same applies to side effects (massive hemorrhage vs small drop in hematocrit)</td>
</tr>
<tr>
<td>Data source</td>
<td>Randomized clinical trials, observational studies, or computer modeling of a hypothetical “cohort” of simulated patients; head-to-head comparisons vs indirect comparisons (treatment A compared with treatment B, vs treatment A compared with placebo and treatment B vs placebo)</td>
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</table>

Methodological Considerations

Studies of the cost-effectiveness of anticoagulants for VTE prophylaxis share a number of methodological features that can exert a strong impact on their outcomes (Table 1). These factors must be kept in mind when evaluating studies describing the clinical and economic impact of drugs for preventing VTE. The studies reviewed herein are summarized in Table 2.2–16 Some critical methodological considerations are briefly described below.

Research Perspective

A common issue in cost-effectiveness studies in health care is the question of whose perspective is taken when the analysis is conducted: that of the acute-care hospital, the payer, the patient, or the health care system as a whole. These distinctions are particularly important in the anticoagulation setting, because LMWHs can be administered on an outpatient basis, sharply reducing expenditures for the hospital but potentially increasing them greatly for patients, particularly those who lack adequate insurance to cover the cost of the drug. Similarly, within the hospital, the costs of an anticoagulant regimen may be borne by the service in which it is administered (eg, orthopedic surgery) or attributed to “the pharmacy budget,” whereas the adverse outcomes associated with treatment (ie, hemorrhage) as well as the benefits from its use (prevention of deep vein thrombosis [DVT] or pulmonary embolism [PE]) may affect expenditures in another part of the hospital (eg, the department of medicine). Thus, it is important to be certain that all costs of a given therapy are taken into account and allocated to the appropriate domain. For example, the cost of international normalized ratio (INR) testing, which can be significant, must be included in the total price of warfarin use, just as the cost of partial thromboplastin time testing must be attached to the expense of full-dose UFH therapy.

For all these reasons, the most appropriate perspective from which to perform cost-effectiveness analyses of VTE prophylaxis is that of society as a whole. Although such analyses may be less appealing to those with a narrower perspective (eg, those seeking to reduce the pharmacy budget or contain the cost of inpatient care), this approach provides the most comprehensive view of the total benefits, risks, and costs attributable to a particular treatment.

Limitations of Trial Data

Data from randomized clinical trials often describe time-frames much shorter than those that interest patients, physicians, and health economists. In the case of VTE research, this requires either consideration of artificially short time horizons (eg, only outcomes that occurred during a given hospitalization) or extrapolation of future benefits and risks months or years beyond the period studied during the trial. This issue is particularly important when assessing the frequency and impact of certain conditions, such as the pulmonary and cardiovascular sequelae of nonfatal PE or the development of post-thrombotic syndrome (PTS).

Another important concern in generalizing trial data to the usual clinical setting is that the study subjects are likely to receive a higher level of monitoring and surveillance than typical patients. This has been referred to as the difference between a drug’s efficacy (its ideal performance in the closely supervised clinical trial context) and its effectiveness (the drug’s outcomes when used by average physicians in routine health care settings). For instance, the safety of warfarin is far better in clinical trial settings than in typical outpatient use, where INR measurements and dose adjustments are less likely to be optimally performed. Similarly, in clinical trials, patients given the new oral anticoagulant ximelagatran were frequently screened, allowing prompt discovery of abnormal transaminase elevations, which led to discontinuation of the drug and close follow-up. It is impossible to know how faithfully this protocol is likely to be followed in routine practice. For cost-effectiveness analyses, the actual “safety” of an agent should be based on the rate of specific adverse events in typical use rather than in the more closely supervised, and hence more artificial, clinical trial environment.

Definition of Outcomes

Studies of prophylactic anticoagulants may have multiple outcomes: hemorrhages can be small or life threatening, and failure of prophylaxis can be manifested by events ranging from massive PE or the development of severe symptomatic thrombophlebitis to the appearance of asymptomatic distal venous thrombosis ascertainable only through special studies. Each of these events has dramatically different clinical and economic impacts. Therefore, it is crucial to closely examine how such outcomes are specified and aggregated in cost-effectiveness studies of VTE prophylaxis. For example, was failure of prophylaxis accounted for exclusively by an increased incidence of asymptomatic distal venous thrombosis or by a difference in the rate of PE? Although the former may represent a relevant outcome, it clearly is less important than the latter.

For these reasons, pharmacoeconomic analyses of anticoagulant performance that calculate results in terms of cost per event prevented are less useful if the nomenclature inappropriately lumps together minor and severe clinical outcomes.
<table>
<thead>
<tr>
<th>Author</th>
<th>Patients at Risk</th>
<th>Perspective</th>
<th>Comparisons</th>
<th>Outcome</th>
<th>Authors' Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Brien</td>
<td>THR</td>
<td>Canadian health care system</td>
<td>Warfarin vs enoxaparin 60 mg</td>
<td>DVT confirmed by bilateral venography</td>
<td>Moderate to strong evidence for adoption of enoxaparin</td>
</tr>
<tr>
<td>Menzin</td>
<td>THR</td>
<td>Hospital</td>
<td>No prophylaxis vs warfarin vs enoxaparin 60 mg</td>
<td>DVT based on clinical diagnosis alone</td>
<td>Cost-effectiveness of enoxaparin compares favorably with other generally accepted medical interventions</td>
</tr>
<tr>
<td>Bergqvist</td>
<td>THR, general surgery</td>
<td>Hospital</td>
<td>No prophylaxis vs treatment upon DVT vs UFH vs LMWH</td>
<td>DVT based on clinical diagnosis alone</td>
<td>General prophylaxis with LMWH more cost-effective than with LDUH</td>
</tr>
<tr>
<td>Borris</td>
<td>THR</td>
<td>Danish health care system</td>
<td>No prophylaxis vs dextran 70 vs LDUH vs LMWH</td>
<td>DVT based on clinical diagnosis alone</td>
<td>Routine thromboprophylaxis with LMWH is more cost effective</td>
</tr>
<tr>
<td>Hull</td>
<td>THR/TKR</td>
<td>Canadian, USA health care systems</td>
<td>Warfarin vs tinzaparin 75 anti-Xa U/kg</td>
<td>DVT confirmed by bilateral venography</td>
<td>Canada: tinzaparin is cost saving; US: inconclusive</td>
</tr>
<tr>
<td>Hawkins</td>
<td>THR</td>
<td>Hospital</td>
<td>UFH 15,000 U/d vs enoxaparin 60 mg</td>
<td>DVT confirmed by bilateral venography</td>
<td>Enoxaparin more cost-effective in avoiding DVT than heparin</td>
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<tr>
<td>Marchetti</td>
<td>THR</td>
<td>Societal</td>
<td>UFH 15,000 U/d vs enoxaparin 40 mg</td>
<td>DVT confirmed by bilateral venography</td>
<td>LMWH a dominant choice relative to UFH</td>
</tr>
<tr>
<td>Devlin</td>
<td>Trauma</td>
<td>Integrated health system</td>
<td>UFH 10,000 U/d vs enoxaparin 60 mg</td>
<td>DVT confirmed by bilateral venography</td>
<td>Enoxaparin cost-effective</td>
</tr>
<tr>
<td>Velmahos</td>
<td>Trauma</td>
<td>Societal</td>
<td>Compression devices vs low-dose UFH vs LMWH vs no intervention</td>
<td>DVT confirmed by duplex ultrasonography</td>
<td>LDUH more cost-effective than LMWH, compression devices, or no intervention</td>
</tr>
<tr>
<td>Sarasin</td>
<td>General surgery</td>
<td>Health care system</td>
<td>Self-administered prophylactic LMWH vs UFH after clinical VTE</td>
<td>DVT based on clinical diagnosis alone</td>
<td>Routine prophylactic anticoagulation with low-dose LMWH should not be recommended</td>
</tr>
<tr>
<td>Mamdani</td>
<td>Elective abdominal surgery</td>
<td>Institutional perspective</td>
<td>No prophylaxis vs pneumatic compression vs UFH 10,000 U/d vs dalteparin 2500 U/d</td>
<td>DVT based on clinical diagnosis alone</td>
<td>Low-dose heparin provides the most cost-effective prophylaxis</td>
</tr>
<tr>
<td>Etchells</td>
<td>Colorectal surgery</td>
<td>Third-party payer</td>
<td>UFH 15,000 U/d vs enoxaparin 40 mg</td>
<td>DVT based on clinical diagnosis alone</td>
<td>Low-dose heparin more economically attractive than enoxaparin</td>
</tr>
<tr>
<td>Samama</td>
<td>Acutely ill medical patients</td>
<td>Hospital</td>
<td>Prophylaxis vs enoxaparin 20 mg or 40 mg</td>
<td>DVT confirmed by bilateral venography or duplex ultrasonography</td>
<td>Prophylactic treatment of 40 mg of enoxaparin subcutaneously per day safely reduces risk of VTE</td>
</tr>
<tr>
<td>de Lissioyv</td>
<td>Seriously ill medical patients</td>
<td>Third-party payer</td>
<td>No prophylaxis vs enoxaparin 40 mg</td>
<td>DVT confirmed by bilateral venography</td>
<td>Prophylaxis cost-effective in terms of incremental cost per VTE avoided</td>
</tr>
<tr>
<td>Nuijten</td>
<td>Seriously ill medical patients</td>
<td>Italian health care system</td>
<td>No prophylaxis vs enoxaparin 40 mg</td>
<td>DVT confirmed by bilateral venography</td>
<td>Thromboprophylaxis with enoxaparin in patients with acute medical illness may be justified from a health economic perspective</td>
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</table>

LDUH indicates low-dose unfractionated heparin; THR, total hip replacement; TKR, total knee replacement.
An example is the incidence of hemorrhagic events. Is a difference in the rate of hemorrhagic events primarily attributable to a higher proportion of patients requiring 1 or 2 U of red cell transfusions, or by life-threatening bleeding events, or intracerebral hemorrhage? A reduction in the rate of severe bleeding complications might justify a substantially higher cost of treatment, but that argument loses weight if the difference in hemorrhagic complications is caused primarily by more modest episodes characterized as abnormal bleeding.

Quantifying Costs
One might suppose that costs would be readily quantifiable in economic analyses; however, this is far from the case. Drug costs can vary substantially from country to country, so that a study performed in one health care system may not be applicable to another. The same is true for the cost of care with adverse clinical outcomes, such as PE or severe hemorrhage. As with the costs of drugs, these expenditures tend to be substantially higher in the United States than in most other health care systems.

A well-conducted cost-effectiveness analysis will clearly specify the economic inputs used for each variable, and will provide information for sensitivity analyses when these expenses are varied to demonstrate the effect of such changes on the output of the study. Similarly, economic assessments should clearly describe how the complex issue of discounting over time was handled. This is usually performed at a rate of 3% per year for both costs and benefits, but practices vary substantially. The discounting rate chosen can have an important effect on the results of the analysis, particularly for treatments administered over the long term or for adverse outcomes that occur years in the future.

Patient Stratification
Because the efficacy and safety of a drug varies in patients with different clinical characteristics, the economic performance of a given anticoagulant regimen varies as well. For example, the cost-effectiveness of a particular prophylactic drug in patients at very high risk for VTE is different than it would be in low-risk patients. Any variable (eg, age, prior medical history, ability to adhere to a demanding regimen, or preexisting coagulation abnormality) that influences the efficacy or safety of an anticoagulant will affect its cost-effectiveness as well. Ideally, cost-effectiveness studies will consider such possibilities a priori, so that stratified analyses can be performed if there is adequate data from clinical trials or observational studies. Such information helps target therapies to patients with characteristics most likely to result in favorable benefit-risk-cost relationships.

Reader Accessibility
Many cost-effectiveness analyses are conducted using complex computer-generated models that simulate hypothetical cohorts of patients. Of necessity, these models are based on simplifying assumptions. The number of parameters may be large, including absolute and relative rates of disease occurrence, transition probabilities, costs, conversion factors, discounting rates, and many others. To make the report accessible to readers, the authors have to strike a balance between sufficient versus excessive presentation of such information. As a result, it is sometimes difficult to assess the adequacy of a study’s assumptions and variables, which can result in a black box problem in judging the origins and validity of the results. This may be particularly relevant when a stakeholder, such as the manufacturer of the drug being analyzed, provides sponsorship of economic evaluations.

Orthopedic Surgery
One of the first cost-effectiveness analyses of primary prevention of DVT was published in 1994. The LMWH enoxaparin had recently been introduced; clinical trials suggested that it was more effective than older treatments in preventing DVT after hip replacement, without an increase in anticoagulant-related side effects. During the same period, Canadian provincial authorities were beginning to seek information on cost-effectiveness of treatments, as well as the conventional measures of efficacy and safety. The concern was heightened in this instance because the ingredient cost of enoxaparin was $60 greater than that of warfarin. Prior studies had compared enoxaparin with heparin, but no data were available from trials that had randomly assigned patients to receive either warfarin or enoxaparin. O’Brien et al therefore identified 10 clinical trials in which each agent had been compared separately with placebo. Their pooled analysis confirmed that the rate of DVT after total hip replacement appeared to be lower with enoxaparin (13.6%) compared with warfarin (20.6%). The cost of care with enoxaparin was $121 more than with warfarin, although it is unclear whether the cost of monitoring was included in the warfarin expense. However, O’Brien et al concluded that in a hypothetical cohort of 10,000 patients, the greater efficacy of enoxaparin relative to warfarin would be expected to prevent 47 more cases of DVT, 3 cases of PE, and 4 deaths. They calculated that an enoxaparin-only strategy would achieve these clinical benefits at a cost of $29,120 Canadian dollars per life-year gained. Their model included the costs of caring for thromboembolic disease and the changes in life expectancy that would result from differences in the rates of these events; however, it did not account for the clinical or economic consequence of side effects, assuming they would be identical in both groups.

There is no absolute guideline for what constitutes an acceptable cost per life-year gained in a given health care system. However, many authors have pointed out that a large number of therapies that are considered standard practice (eg, hemodialysis for end-stage renal disease, drugs for managing hypertension, treatment of hypercholesterolemia in appropriately selected at-risk patients) yield incremental cost-effectiveness ratios that require $50,000 or less to gain an additional quality-adjusted life-year. Using this benchmark, O’Brien et al concluded that the additional expense of enoxaparin use was probably within the range of what the health care system would consider “cost-effective.” They cautioned that this determination was tentative as there were no head-to-head studies comparing the regimens being studied.

The same question was addressed the following year by Menzin et al, who took a similar approach to comparing
enoxaparin with low-dose warfarin for DVT prophylaxis after total hip replacement. Like O’Brien et al, the study reviewed the existing literature to predict the clinical course in a hypothetical cohort of 10,000 patients treated either with no prophylaxis, low-dose warfarin, or enoxaparin. Data from randomized trials were used to predict the frequency of specific events such as hemorrhagic complications or failure of prophylaxis; costs of care were based on the amounts routinely reimbursed for specific services and drugs in the United States at that time.

In this study, the total expected costs for all care were highest for the group of patients who underwent no prophylaxis ($5,327,000) than for either of the anticoagulant groups. This was attributed to the substantial costs associated with subsequent care for a higher number of patients with DVT or PE. For the 2 prophylaxis arms of the decision tree, the projected aggregate cost for enoxaparin ($2,140,800) was substantially higher than that for warfarin ($776,800). However, the cost of diagnosing and treating thromboembolic complications was predicted to be 50% higher in the warfarin group than in the enoxaparin group. As a result, the total costs of care were similar in the treatment arms ($3,787,400 for enoxaparin versus $3,259,000 for warfarin). Because patients in the enoxaparin arm would be expected to have a smaller number of thromboembolic deaths, the authors concluded that the incremental cost of enoxaparin amounted to only $12,288 per death averted, which compared favorably with the cost-effectiveness of other generally accepted medical interventions. The analysis did not take into account potential differences in rates of bleeding or the cost of treating recurring DVT or PTS.

Bergqvist et al modeled different treatment approaches for preventing DVT in patients undergoing elective hip surgery or general abdominal surgery. The strategies considered were no prophylaxis, selective treatment of DVT only after it was diagnosed, and routine prophylaxis in all patients with low-dose UFH and various LMWH products. Their model was based on data for the rates of thromboembolism and hemorrhage reported in 3 review articles. Considering the total cost of care for events occurring in-hospital, they found that the no-prophylaxis and treat-after-diagnosis strategies were the most costly. Routine prophylaxis was least expensive, with LMWH somewhat less costly than low-dose UFH. Several variables were ignored in this analysis, including the cost of mortality, post-thrombotic complications such as venous insufficiency, and the possibility that patients on the LMWH regimen could have been treated outside of the hospital for part of the time. Had they been considered, these factors would have further favored the LMWH strategy over the others, including low-dose UFH.

Similar conclusions were reached by another Scandinavian team, Borris and Lassen. Based on the clinical literature, they developed a decision tree to predict the costs of care of patients undergoing total hip replacement who received either LMWH, dextran, low-dose UFH, or no prophylaxis. Their findings illustrate the enormous impact that local economic factors can have on the results of such analyses. In Danish Kroner (DKK), cost for 8 days of LMWH therapy was 372 DKK compared with 326 DKK for 8 days of low-dose UFH and 2,000 DKK for monitoring of anticoagulation. Clearly, these findings have limited generalizability to health care systems with quite different combinations of costs.

A similar difficulty arises when attempting to extrapolate Canadian data to the US health care system. This is illustrated in a study performed by Hull et al, who based their calculations on a controlled trial of patients who underwent hip or knee replacement and were then randomly allocated to either the LMWH tinzaparin or warfarin. The rate of DVT was slightly lower in the LMWH group (31.4% versus 37.4%, P = 0.03). The LMWH regimen was less expensive overall as well ($9197 for LMWH versus $11,598 for warfarin; the cost of INR measurement was included in the cost for warfarin). The authors also calculated the cost of delivering the 2 regimens in the United States for the same period. The price of warfarin was 6× greater and complete blood counts were 3× greater in the United States than in Canada. Similarly, the cost of LMWH and the syringes and needles necessary for its administration were nearly threefold greater in the United States than in Canada. Although it is plausible to assume that the rate of complications, whether embolic or hemorrhagic, may be the same cross-nationally, the costs of their treatment will vary from country to country, limiting the applicability of an economic assessment performed in one nation to the health care system of another.

Hawkins et al pooled the results of 3 randomized clinical trials to assess the cost-effectiveness of enoxaparin versus subcutaneous heparin in patients undergoing total hip replacement in the United States. Their analysis included treatment expenses as well as the cost of adverse events; separate tracking was conducted for major bleeding and treatment failure, including proximal DVT, distal DVT, and PE. The investigators found that in calculating the cost of prophylaxis divided by the rate of DVT events avoided, the cost per avoided event was consistently lower for enoxaparin than for subcutaneous heparin; this finding was consistent across the 3 trials despite the higher ingredient cost of the enoxaparin regimen.

Finally, Marchetti et al compared LMWH versus UFH in patients undergoing elective hip replacement in Italy. Based on the acquisition cost of LMWH in that country, they developed a model that projected thromboembolic and hemorrhagic events onto hypothetical cohorts of patients, based on all available English-language trial reports and meta-analyses. The LMWH strategy yielded an increase in quality-adjusted days as well as modest savings over the UFH arm. The authors performed sensitivity analyses for a wide number of variables, concluding that the model outcome was “independent of most parameters.” However, given the national context in which this research was performed, although costs were converted into US dollars, they were, in actuality, much lower than true costs in the United States for several key variables. Prophylaxis over 2 weeks with LMWH was assumed to cost only $63, whereas that for UFH was $61, and the maximum cost modeled in the sensitivity analyses was just $110 for both regimens. Clearly, these findings are not applicable to a health care system such as that of the United States in which the ingredient costs of LMWH are dramatically higher than those of UFH.
Trauma
Two cost-effectiveness analyses evaluated alternative prophylactic regimens in trauma patients. Devlin et al compared the cost-effectiveness of enoxaparin with that of UFH in major trauma patients, using the perspective of an integrated health system. From their decision analysis model of 1000 hypothetical trauma patients, they predicted that 62.2 additional DVT or PE events would be avoided using enoxaparin compared with UFH. This would result in 67.6 life-years saved in 1000 patients, achieved at a net cost increase of $104 764. These findings translated into a cost of $1684 for each DVT or PE avoided, or $2303 per life-year saved.

The authors found an even more favorable cost-effectiveness ratio when restricting their analyses to patients having only lower extremity fractures ($1017 per life-year saved). Sensitivity analyses indicated that the results were highly sensitive to changes in the cost of prolonged hospital stay for DVT or PE. When longer hospitalization was assumed to be completely additive to the index hospitalization, enoxaparin became cost saving. However, in the absence of efficacy data for trauma patients in a routine care setting, the authors extrapolated such data from studies in orthopedic surgery patients.

A more recent study pointed out that even meta-analyses of anticoagulation in trauma patients had failed to reveal an effectiveness benefit for low-dose UFH, LMWH, or sequential compression devices compared with no intervention. Its authors concluded that in the absence of demonstrated effectiveness for any of these interventions, a cost-effectiveness study could not validly be performed, and called for a larger and sufficiently powered comparative clinical trial to establish the relative benefit of these interventions.

Despite this conclusion, the investigators went on to conduct a decision analytical model that compiled input parameters from several sources of highly variable quality, and concluded that low-dose UFH was more cost-effective than the other options. An accompanying editorial comment disputed this summation, suggesting that the evidence allowed for 2 conclusions. First, if the studies of varying quality included in the original meta-analyses were valid, then the preferred option would be to not provide any prophylaxis at all. Alternatively, assuming that several of the studies cited were flawed, the appropriate fallback choice would be to use the findings from the well-conducted randomized trial that demonstrated superior efficacy of LMWH over UFH.

Other Surgery
The first cost-effectiveness analysis of prophylactic anticoagulation on hospital discharge after general surgery was published in 1996. Mamdani et al compared LMWH over 4 weeks after discharge with use of UFH administered after the first clinically overt VTE. They found that the number of VTEs prevented by prophylactic LMWH anticoagulation would exceed the number of major bleeding events prevented if the weekly VTE rate exceeded 0.04%—a rate which will vary depending on the characteristics of the population being treated; in these circumstances there would be a net benefit for this strategy. They further concluded that the marginal cost-effectiveness of an LMWH prevention strategy over waiting to treat VTEs with UFH once they occurred would be $45 353 to $135 903 per VTE averted, depending on the rate of VTE.

In the same year, a detailed cost-effectiveness study compared low-dose heparin, dalteparin, and intermittent pneumatic compression with no prophylaxis in patients undergoing elective abdominal surgery. The analysis was conducted from an institutional perspective. The costs per complication-free patient were $86 (heparin), $103 (intermittent pneumatic compression), $118 (no prophylaxis), and $124 (dalteparin). When the measurement was expressed as the cost per mortality prevented, both heparin and intermittent pneumatic compression were cost saving compared with no prophylaxis, whereas dalteparin incurred a modest cost of $2857 per mortality avoided.

The perspective of a third-party payer was taken in a cost-effectiveness analysis comparing 7 days of perioperative prophylaxis with either low-dose UFH or enoxaparin in patients undergoing colorectal surgery. Based on clinical trial data, Etchells et al assumed both prophylactic strategies had equal efficacy in preventing DVT and PE, whereas enoxaparin was assumed to have a 1.8-fold increased risk for major bleeding compared with low-dose UFH. The authors found that low-dose UFH was equally effective, safer, and less costly than enoxaparin. In extensive sensitivity analyses exploring several scenarios using parameters highly favorable to enoxaparin, the resulting cost-effectiveness ratios still were found to be economically unattractive for LMWH prophylaxis.

Medical Patients
The potential role for VTE prophylaxis in hospitalized patients took an important turn with the publication in 1999 of the MEDical patients with ENOXaparin (MEDENOX) trial. This randomized, double-blind trial compared prophylaxis with 20 mg (n = 364) or 40 mg (n = 367) enoxaparin with placebo (n = 371) in acutely ill hospitalized medical patients. The chief study end point was the incidence of VTE events between days 1 and 14 after randomization. Only 5.5% of patients randomized to 40 mg enoxaparin had a VTE event during this period compared with 14.9% of patients receiving placebo (P < 0.001). The outcomes observed in the 20 mg enoxaparin group were not different from those seen with placebo.

Several pharmacoeconomic analyses were subsequently conducted that estimated the cost-effectiveness implications of the MEDENOX study from the perspective of various national health care systems. De Lissovoy and Subedi considered the data from the perspective of a third-party payer, calculating the use of enoxaparin would cost between $1249 and $3088 per VTE episode avoided. Similarly, Nuijten et al assessed the cost-effectiveness of this same intervention from the perspective of the Italian National Health Service. Using a different analytic approach, they calculated that the cost per VTE event avoided was €2451, whereas that per life saved was €8396, both in comparison with no treatment. The incremental cost per life year gained was estimated at just €605.
The results of these analyses must be considered in light of several controversies. Most prominent are the concerns that were raised regarding the MEDENOX study. An objection made on ethical grounds\(^2\) also has important implications for cost-effectiveness analyses of this trial. Sosin\(^2\) objected to the choice of placebo as the comparison treatment in MEDENOX, arguing that the authors expected 15% of the untreated patients to experience thromboembolic events, and that it was therefore improper to randomize any of them to placebo. The MEDENOX investigators replied that equipoise was appropriate at the time of their study, because at that point there was no consensus that hospitalized medical patients should be anticoagulated to prevent thromboembolic complications.\(^3\) In fact, the trialists argued, in the absence of evidence for efficacy, it would have been unethical to allocate all patients in the study to a potentially hazardous treatment such as anticoagulation, a plausible position.

Apart from the pros and cons of the ethical arguments, the comparison with placebo only, as opposed to a relatively inexpensive alternative treatment, such as UFH, does raise important concerns regarding the cost-effectiveness analyses of the MEDENOX study. The trial only indicated whether LMWH was better than no treatment, shedding no light on its efficacy compared with another anticoagulant strategy. Similarly, the cost-effectiveness analyses based on it can only predict the relative cost-effectiveness of enoxaparin compared with no treatment, revealing no information about how it compares with other therapies, such as heparin.

The majority of events prevented by enoxaparin in MEDENOX were distal DVT (62% of events prevented).\(^2\) Thus, although enoxaparin was shown to significantly reduce thromboembolic events, the interpretation of the meaning of “cost per event prevented” in the follow-up pharmacoeconomic analyses should include the caveat that these events were primarily episodes of distal DVT, rather than proximal DVT or PE.

Pharmacoeconomic analyses often must consider end points that the underlying clinical trial lacked power to measure precisely. This is the case with mortality in the MEDENOX study. Although the graphed survival curves presented in the original report depicted a striking separation of the mortality rate for patients randomized to 40 mg enoxaparin compared with placebo, this difference was far from statistically significant (95% confidence interval, 0.56 to 1.21; \(P=0.3\)). The original study was not sufficiently powered to detect a significant difference in the mortality rate between groups. It is important to consider the relative strength of the evidence underlying measures such as “cost per life saved,” as pharmacoeconomic analyses often are obliged to make determinations on end points for which the original trial was not adequately powered.

### Conclusion

The coming years hold considerable promise for wider and more appropriate use of anticoagulants to prevent the potentially disastrous complications of VTE. Pulmonary embolus still represents the most common preventable cause of death in hospitalized patients; the number of appropriate candidates for such treatment may be much larger than previously thought. At the same time, the introduction of new classes of treatment, such as the direct thrombin inhibitors, presents clinicians and the health care system with additional therapeutic choices. Moreover, the aging of the population is producing growing numbers of patients requiring hospitalization for acute medical illness or surgery for the most common orthopedic sequelae of aging, hip fractures, and the need for joint replacement. This demographic imperative as well as the expanded indications for thromboprophylaxis in nonsurgical patients and the high cost of newer agents make the need for systematic assessment of the cost-effectiveness of these regimens more pressing with each year.

The cost-effectiveness of a particular medication is not a permanent and fixed property of a given molecule, but varies depending on the patients in whom it is used, their underlying need for the therapy, and their propensity for adverse events.\(^3\) For this reason, different regimens are likely to have different cost-effectiveness ratios in various patient subgroups, as is the case in cardiovascular medicine. Thus, the agenda for research into cost-effectiveness is long and expanding. Unless health care resources suddenly become infinite, it is an agenda that must be aggressively pursued to provide the most appropriate anticoagulant care to the largest number of patients.

Prevention of thromboembolic disease increasingly resembles a familiar scenario for many cardiovascular drugs: the widespread use of medications to manage “risk states” rather than treat acute problems. This group of medications, which includes statins, beta-blockers after acute myocardial infarction, and antihypertensive drugs, accounts for most prescriptions in the United States, and, thus, most drug expenditures. Rising pharmaceutical costs in conjunction with growing pressure on economic resources for all forms of medical care will mandate rigorous definition of the relationship among cost, benefit, and safety in preventing VTE.

### References


Comparing the Costs, Risks, and Benefits of Competing Strategies for the Primary Prevention of Venous Thromboembolism
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