

# Cost Effectiveness of Thromboprophylaxis With a Low-Molecular-Weight Heparin Versus Unfractionated Heparin in Acutely Ill Medical Inpatients

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**Objective:** To compare the cost effectiveness of prophylaxis with a low-molecular-weight heparin with that of prophylaxis with unfractionated heparin for the prevention of venous thromboembolism in acutely ill medical inpatients.

**Study Design:** Cost-effectiveness analysis based on decision-tree model.

**Participants and Methods:** A hypothetical cohort of 10 000 patients was assumed to receive either (1) prophylaxis with enoxaparin, a low-molecular-weight heparin, 40 mg daily; (2) prophylaxis with unfractionated heparin, 5000 IU twice daily; or (3) no prophylaxis. We developed a decision-analytic model with parameter estimates derived from published clinical trials and other secondary sources. Then, for each strategy, we estimated the risks of venous thromboembolism, complications of prophylaxis and treatment (heparin-induced thrombocytopenia and bleeding), mortality, and costs of prophylaxis and treatment within a 30-day period.

**Results:** In a hypothetical cohort of 10 000 inpatients, expected numbers of deaths attributable to venous thromboembolism or drug complications related to both prophylaxis and treatment of VTE over a 30-day period were 37 with enoxaparin prophylaxis, 53 with unfractionated heparin prophylaxis, and 81 with no prophylaxis. In 2001, corresponding expected costs of prevention, diagnosis, and management of VTE were \$3 502 000 for enoxaparin, \$3 772 000 for unfractionated heparin, and \$3 105 000 for no prophylaxis. The incremental cost per death averted with enoxaparin prophylaxis versus no prophylaxis was \$9100. Enoxaparin dominated unfractionated heparin by being both more effective and less costly in the base-case analysis, as well as in sensitivity analyses in which equal efficacy and equal risks of bleeding were assumed.

**Conclusions:** Thromboprophylaxis with this low-molecular-weight heparin represents a cost-effective use of healthcare resources in acutely ill medical inpatients and dominates thromboprophylaxis with unfractionated heparin.

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Several subgroups of hospitalized patients are at elevated risk for VTE, including those undergoing orthopedic or other major surgery, as well as those with acute circulatory conditions such as myocardial infarction, atrial fibrillation, angina, or thrombotic stroke. The Sixth ACCP Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis recommend thromboprophylaxis as standard practice for these patients.<sup>2</sup> In recent years, the substantial risk of VTE in the general medical population has emerged as an important clinical concern also.<sup>3</sup> Acutely ill medical inpatients, such as those hospitalized for congestive heart failure, chronic obstructive pulmonary disease, or acute infections, often have hypercoagulability and periods of prolonged immobility that may place them at increased risk of VTE.<sup>2,4</sup> Because these patients are likely to have one or more additional risk factors (eg, history of VTE, advanced age, obesity, varicose veins, estrogen use),<sup>2</sup> the potential benefits of thromboprophylaxis in this population may be substantial.

As the risk of VTE among general medical patients has gained recognition, the introduction of low-molecular-weight heparin (LMWH) has provided an alternative to thromboprophylaxis with unfractionated heparin (UFH), the previous standard. The efficacy of both LMWH and UFH as thromboprophylaxis in selected groups of medical inpatients has been demonstrated in clinical trials,<sup>5-11</sup> and there is evidence that LMWH may have a better safety profile than UFH with regard to both hemorrhage<sup>6-8</sup> and heparin-induced thrombocytopenia (HIT).<sup>6-7,11</sup> Because LMWH is more costly, however, the question remains whether its use can be justified in

Venous thromboembolism (VTE) is a life-threatening vascular disease common among hospitalized patients. It is estimated that more than 170 000 incident cases of VTE are diagnosed in hospitalized patients in the United States each year, and more than 20 000 of these patients die of the condition before discharge.<sup>1</sup> Because many cases of incident thromboembolism go undetected and untreated, primary prevention in at-risk patients is of critical importance.

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terms of reduced risk of drug-related adverse events and, possibly, improved efficacy. To address this question, we examined the cost effectiveness of prophylaxis with an LMWH, specifically enoxaparin, versus prophylaxis with UFH in acutely ill general medical inpatients.

METHODS

Study Design

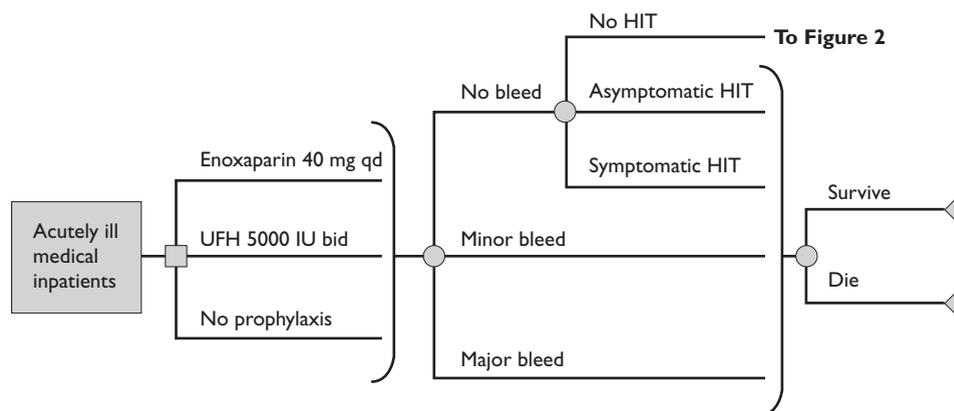
We used techniques of decision analysis and data from secondary sources to develop a model of the prevention, detection, treatment, and outcomes of VTE in general medical patients. A hypothetical cohort of 10 000 acutely ill medical inpatients was assumed to receive one of three methods of thromboprophylaxis: (1) enoxaparin, a representative LMWH (Lovenox; Aventis Pharmaceuticals; Bridgewater, NJ), 40 mg administered subcutaneously once daily; (2) UFH, 5000 IU administered subcutaneously twice daily; or (3) no prophylaxis. Our choice of dosing and frequency of administration reflects current recommendations for thromboprophylaxis in medical patients.<sup>2</sup> For each strategy, we estimated the 30-day risks of VTE, including deep vein thrombosis (DVT) and/or pulmonary embolism (PE); complications of prophylaxis and therapy, such as HIT and bleeding; mortality; and the costs of prophylaxis, diagnostic testing, and treatment. We used these estimates to examine the incremental cost effectiveness of thromboprophylaxis, expressed in terms of the cost per death averted.

Treatment patterns and outcomes of care were modeled for 30 days from the time of hospital admission. This time period was chosen to capture DVT and PE occurring both in the hospital and during the period immediately following discharge, during which time patients may continue to be at elevated risk of VTE. Our analysis was conducted from the perspective of a third-party health insurer and therefore considered only direct medical costs.

Model Structure

The structure of the decision-tree model is illustrated in Figures 1 through 3. The clinical starting point for

Figure 1. Thromboprophylaxis Methods and Related Adverse Events



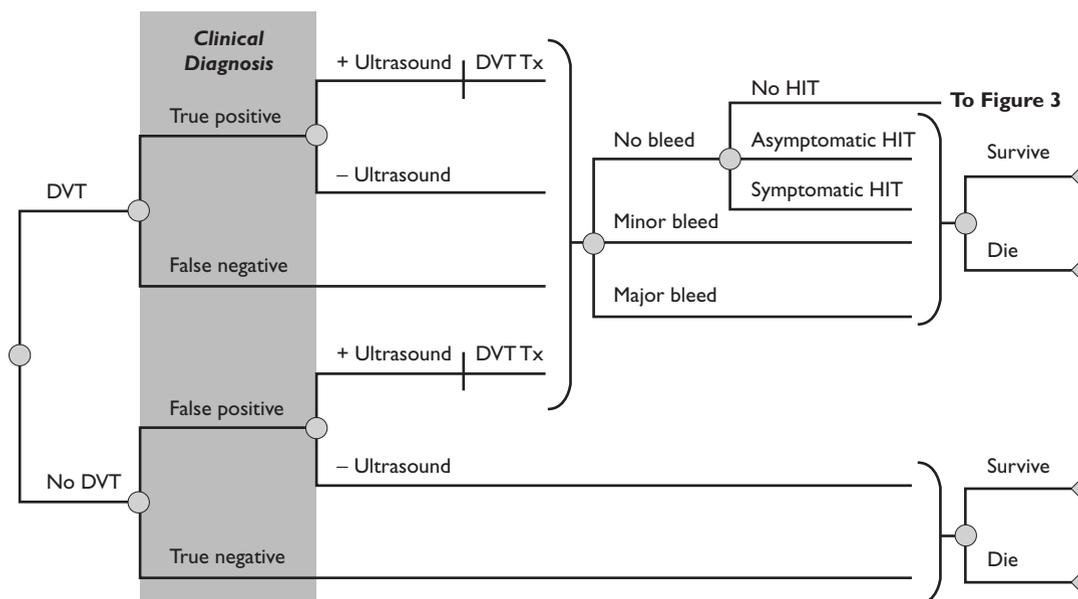
UFH indicates unfractionated heparin; HIT, heparin-induced thrombocytopenia.

the model is admission to an acute-care facility for treatment of a serious medical condition. For these patients, the clinical decision of interest is the method of thromboprophylaxis administered, either enoxaparin, UFH, or no prophylaxis (Figure 1). Patients receiving enoxaparin or UFH are assumed to be at risk for drug-related adverse events, including hemorrhage ("bleed") and HIT. Bleeds may be either minor or major, while HIT is classified as asymptomatic or symptomatic according to the presence or absence of overt clinical symptoms. Major bleeds and symptomatic HIT may lead to death, though for modeling convenience we assumed that patients who survive one of these adverse events are not at risk of additional adverse events or VTE.

Patients who do not experience HIT or hemorrhage are at risk of DVT (Figure 2). Because clinical diagnosis of DVT is imperfect, the tree reflects this uncertainty by allowing patients to receive a true- or false-positive or negative clinical diagnosis. Patients with a positive clinical diagnosis (whether true or false) are referred for duplex ultrasound and, if confirmed, for treatment. Those with a negative clinical diagnosis receive no confirmatory diagnostic procedures or treatment. This model assumes that all patients whose DVT diagnosis is confirmed by ultrasound undergo anticoagulation therapy with enoxaparin; such patients are at risk for bleeds and HIT. Patients who survive treatment-related adverse events, such as bleeds or HIT, finish treatment and are not at risk of further adverse events or PE.

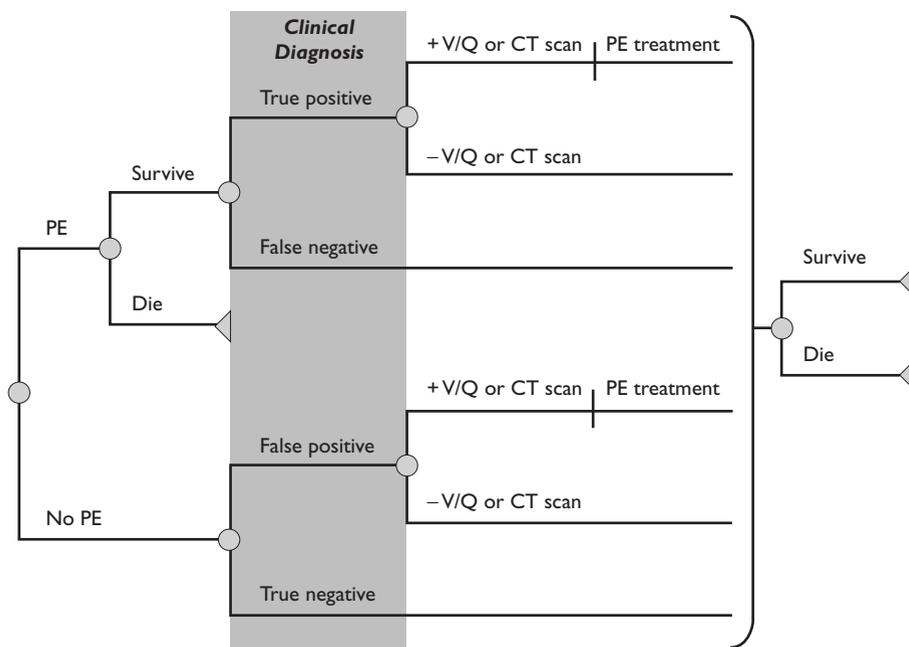
Patients who have DVT and do not experience an adverse event from its treatment are at risk for PE

**Figure 2.** Diagnosis and Management of Deep Vein Thrombosis



DVT indicates deep vein thrombosis; DVT Tx, treatment of DVT; HIT, heparin-induced thrombocytopenia.

**Figure 3.** Diagnosis and Management of Pulmonary Embolism



PE indicates pulmonary embolism; V/Q, ventilation-perfusion; CT, computed tomography.

sis of PE. Patients with a positive clinical diagnosis (whether true or false) are referred for a confirmatory ventilation-perfusion (V/Q) scan or computed tomography (CT) scan and, if positive, for treatment of PE. Patients may die from treated or untreated PE or from other underlying medical conditions.

**Model Estimation**

Model estimation involves assigning probability estimates to each of the model's chance nodes and cost estimates to each pathway. Base-case transition probabilities and data sources are summarized in Table 1.

Risks of failure and the occurrence of adverse events for each prophylaxis

(Figure 3). Patients who experience PE and survive the period immediately after the acute event may be given either a true-positive or a false-negative clinical diagno-

method were obtained from the published literature. We used data from MEDENOX,<sup>10</sup> a recent placebo-controlled clinical trial, in our model, evaluating 40 mg

enoxaparin once daily as thromboprophylaxis in medical patients to estimate the risk of DVT with enoxaparin prophylaxis and the baseline risk of DVT among untreated patients. MEDENOX is the only published placebo-controlled trial of an LMWH that enrolled general medical patients, administered a dose of enoxaparin consistent with current recommendations,<sup>2</sup> and diagnosed DVT using venography. We were unable to identify any published studies that compared an LMWH to either UFH or placebo and met these criteria. Therefore, to estimate the risk of prophylaxis failure among patients receiving UFH, we used the results of a recent meta-analysis of trials that compared LMWH to UFH in medical patients<sup>12</sup> and applied the summary risk-ratio of 0.83 to the risk of prophylaxis failure in the LMWH arm of the MEDENOX trial.

Because HIT and bleeds occurred infrequently in the published trials of thromboprophylaxis in medical inpatients and because their detection does not depend on venography, estimates of the rates of occurrence and severity of these events were drawn from a wider range of clinical trials than those used for the efficacy estimates.<sup>6-8,11</sup> Published estimates of “symptomatic” or “severe” HIT<sup>10,15-18</sup> were assumed to include thrombocytopenia leading to thromboembolism. The other transition probabilities in the model are uniform across all treatment arms, and most were estimated from the published literature. The estimate of the probability of false-negative clinical diagnosis of DVT was derived from studies examining the prevalence of DVT in asymptomatic patients.<sup>29-30</sup> For the base-case analysis, the risk of death due to the underlying medical condition was assumed to be 10%, which is consistent with the rates of death reported in published clinical trials focusing on acutely ill medical inpatients.<sup>6-10,12</sup> Finally, because we assumed that one half of the patients with suspected PE would undergo CT scans and one half V/Q scans, we used the average sensitivity and specificity of these 2 diagnostic techniques in the model. Where multiple data sources were used, estimates were combined across studies by direct pooling.

### Costs

The model's cost parameters include (1) study medications and ancillary resources, (2) laboratory procedures, (3) hospital inpatient days, (4) physician inpatient visits, and (5) physician office/outpatient visits. All cost estimates employed in the analysis are summarized in **Table 2**.

Drug acquisition costs were estimated from average wholesale prices<sup>42</sup>; for the weight-based doses, the total amount of drug used was estimated assuming a 75-kg patient. Cost estimates associated with the supplies

used to administer drugs were obtained from published data.<sup>43</sup> The costs of laboratory procedures for monitoring anticoagulation therapy were estimated using data from the Centers for Medicare & Medicaid Services<sup>44</sup>; and the costs of physician inpatient and office/outpatient visits were estimated using the Medicare Resource-Based Relative Value Scale payment rates.<sup>45</sup> Mean daily inpatient costs attributable to adverse drug reactions and VTE were estimated by dividing the unadjusted payment for deep vein thrombophlebitis (Diagnosis Related Group 128) by the average length of stay for this diagnosis.<sup>46</sup>

Although our primary focus was on costs incurred within 30 days of hospital admission, we included costs after 30 days if they were incurred as a direct consequence of events within the first 30 days (eg, 6 months of warfarin therapy following DVT). All costs were measured in 2001 US dollars; where necessary, costs were updated to 2001 using the medical-care component of the Consumer Price Index.<sup>47</sup> Because of the brief time horizon of the model, discounting was not required.

### Analyses

For each of the 3 prophylaxis methods being evaluated, we used our model to estimate the total costs of prevention, detection, treatment, and outcomes of VTE in a cohort of 10 000 acutely ill medical inpatients over a 30-day period. Cost effectiveness is expressed in terms of the cost per death averted. To compare treatment strategies we first rank-ordered regimens by increasing cost and eliminated those strategies that were found both more costly and less effective than (*dominated* by) others. For each remaining strategy we then calculated the additional cost and additional deaths averted versus the next lowest cost strategy. The ratio of these 2 numbers (ie, the incremental cost per death averted) is the incremental cost-effectiveness ratio.

Sensitivity analyses were performed to assess the robustness of key model parameters and to evaluate the effect of alternative assumptions on model outcomes. To explore the cost effectiveness of thromboprophylaxis in patients with different comorbidity and risk profiles, we analyzed subgroups of patients from the MEDENOX trial with heart failure, respiratory disease, or infectious disease.<sup>48</sup> We varied the background death rate and the underlying risk of DVT in patients receiving no prophylaxis, as well as the relative safety and efficacy of the 2 active prophylaxis arms. Lastly, we examined the effect on our findings of changing assumptions about the cost of drug therapy, risk of bleeding due to prophylaxis, progression from DVT to PE, and death from PE.

CLINICAL

**Table 1.** Base-case Transition Probabilities, by Method of Prophylaxis

Model Parameter	Enoxaparin 40 mg qd	UFH 5000 IU BID	No Prophylaxis	Source
<b>Efficacy and Safety of Prophylaxis:</b>				
P{DVT}	0.055	0.066	0.142	Mismetti 2000, <sup>12</sup> Samama 1999 <sup>10</sup>
P{bleed}	0.031	0.058	0.020	Bergmann 1996, <sup>6</sup> Harenberg 1996, <sup>7</sup> Lechler 1996, <sup>8</sup> Samama 1999 <sup>10</sup>
P{HIT}	0.001	0.010	0.000	Warkentin 1995, <sup>11</sup> Bergmann 1996, <sup>6</sup> Harenberg 1996, <sup>7</sup> Samama 1999 <sup>10</sup>
<b>Consequences of Adverse Events:</b>				
P{major bleed bleed}	0.185	0.185	0.185	Bergmann 1996, <sup>6</sup> Harenberg 1996, <sup>7</sup> Lechler 1996, <sup>8</sup> Samama 1999, <sup>10</sup> Shaieb 1999 <sup>13</sup>
P{death major bleed}	0.148	0.148	0.148	Levine 2001 <sup>14</sup>
P{symptomatic HIT HIT}	0.543	0.543	0.543	Warkentin 1996, <sup>15</sup> Nand 1997, <sup>16</sup> Kahl 1998, <sup>17</sup> Samama 1999, <sup>10</sup> Warkentin 2000 <sup>18</sup>
P{death symptomatic HIT}	0.098	0.098	0.098	Greinacher 1999 <sup>19</sup>
<b>Efficacy and Safety of DVT Tx:</b>				
P{bleed DVT tx}	0.083	0.083	0.083	Dolovich 2000, <sup>20</sup> Merli 2001 <sup>21</sup>
P{HIT DVT tx}	0.012	0.012	0.012	Dolovich 2000, <sup>20</sup> Merli 2001 <sup>21</sup>
P{PE DVT tx, DVT}	0.018	0.018	0.018	Dolovich 2000, <sup>20</sup> Merli 2001 <sup>21</sup>
<b>Efficacy and Safety of PE Tx:</b>				
P{death PE Tx, +PE}	0.015	0.015	0.015	Douketis 1998 <sup>22</sup>
P{death PE Tx, -PE}	0.003	0.003	0.003	Simonneau 1997 <sup>23</sup>
<b>Natural History:</b>				
P{sudden death PE}	0.100	0.100	0.100	Dalen 1975, <sup>24</sup> Bell 1982 <sup>25</sup>
P{PE no DVT tx, DVT}	0.511	0.511	0.511	Huisman 1989, <sup>26</sup> Moser 1994 <sup>27</sup>
P{death no PE tx, PE}	0.260	0.260	0.260	Baritt 1960 <sup>28</sup>
P{death underlying illness}	0.100	0.100	0.100	Assumption
<b>Diagnosis of DVT:</b>				
P{+clinical diagnosis +DVT}	0.657	0.657	0.657	]— Lucchi 1993, <sup>29</sup> Diamond 1997 <sup>30</sup>
P{-clinical diagnosis -DVT}	0.869	0.869	0.869	
P{+ultrasound +DVT}	0.960	0.960	0.960	]— Mitchell 1991, <sup>31</sup> Quintavalla 1992, <sup>32</sup> Kennedy 1999 <sup>33</sup>
P{-ultrasound -DVT}	0.962	0.962	0.962	
<b>Diagnosis of PE:</b>				
P{+ clinical diagnosis +PE}	0.291	0.291	0.291	PIOPED Investigators 1990, <sup>34</sup> Moser 1994, <sup>27</sup> Goodman 1995, <sup>35</sup> Teigen 1995, <sup>36</sup> Mandelli 1997, <sup>37</sup> Kim 1999, <sup>38</sup> Velmahos 2001 <sup>39</sup>
P{-clinical diagnosis -PE}	0.910	0.910	0.910	PIOPED Investigators 1990 <sup>34</sup>
P{+CT scan +PE}	0.760	0.760	0.760	]— Harvey 2000, <sup>40</sup> Perrier 2001, <sup>41</sup> Velmahos 2001 <sup>39</sup>
P{-CT scan -PE}	0.894	0.894	0.894	
P{+V/Q scan +PE}	0.410	0.410	0.410	]— PIOPED Investigators 1990 <sup>34</sup>
P{-V/Q scan -PE}	0.970	0.970	0.970	
P{+scan (average) +PE}	0.585	0.585	0.585	]— Average of CT scan and V/Q scan
P{-scan (average) -PE}	0.932	0.932	0.932	

LMWH indicates low-molecular-weight heparin; UFH, unfractionated heparin; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; CT, computed tomography; V/Q, ventilation-perfusion.

**Table 2.** Base-case Cost Estimates

Cost Item	Estimate (\$)	Notes
<b>5 days of prophylaxis:</b>		
UFH 5000 IU bid	112	Average wholesale price of \$1.15 for 5000-IU prefilled syringe* plus \$10 in pharmacy and nursing costs assumed per administration
Enoxaparin 40 mg qd	172	Average wholesale price of \$24.46 for 40-mg prefilled syringe* plus \$10 in pharmacy and nursing costs assumed per administration
<b>Adverse events:</b>		
Minor bleed	611	Assume 1 additional hospital day (\$553.25) based on average reimbursement per day for deep vein thrombophlebitis (DRG 128) <sup>†</sup> plus 1 additional physician inpatient visit (\$57.39): subsequent hospital care, moderate complexity (CPT 99232) <sup>‡</sup>
Major bleed	3565	Assume 5 additional hospital days (\$2766.23), 5 additional physician inpatient visits (\$286.95), blood transfusion service (\$35.58) (CPT 36430), <sup>‡</sup> 2 units packed red blood cells (\$260), complete blood count (\$58.50) (CPT 85024), <sup>§</sup> and 2 additional outpatient visits (\$157.62): established patient, moderate complexity (CPT 99214) <sup>‡</sup>
Asymptomatic HIT	611	Assume 1 additional hospital day (\$553.25) plus 1 additional physician inpatient visit (\$57.39)
Symptomatic HIT	8843	Assume 7 additional hospital days (\$3872.73), 7 additional physician inpatient visits (\$401.73), 7 days partial thromboplastin monitoring (\$58.10) (CPT 85730), <sup>§</sup> initial bolus of lepirudin [including 50-mg vial (\$131.04),*, syringes and needles (\$1.17), <sup>  </sup> phlebotomy (\$17.98)], 5 days IV treatment with lepirudin [including daily: 6 50-mg vials (\$786.24), dextrose 5% 500 mL (\$11.80),* IV catheter (\$3.96), <sup>  </sup> tubing (\$1.30), <sup>  </sup> pump (\$4.22), <sup>  </sup> phlebotomy (\$17.98)], 6 months of warfarin therapy including daily 5-mg warfarin (\$0.57)* and weekly prothrombin time tests (\$5.43) (CPT 85610) <sup>§</sup>
<b>Costs of diagnosis:</b>		
DVT	268	Assume 1 additional physician inpatient visit (\$57.39) plus ultrasound (\$210.42) (CPT 93970) <sup>‡</sup>
PE	324	Assume 1 additional physician inpatient visit (\$57.39) plus CT scan (\$350.83) (CPT 71260) <sup>‡</sup> or V/Q scan (\$182.79) (CPT 78584) <sup>‡</sup>
<b>Cost of treatment:</b>		
DVT	2045	Assume 2/3 of patients treated inpatient [including 5 days of therapy with 1 mg/kg enoxaparin bid for patient weighing 75 kg (\$489.20), 2 additional hospital days (\$1106.49), 5 additional physician inpatient visits (\$286.94), 5 physician office/outpatient visits (\$394.06), 6 months of warfarin therapy (\$232.92)] and 1/3 treated outpatient [including 5 days of enoxaparin therapy (\$489.20), 5 additional office/outpatient visits (\$394.06), and 6 months of warfarin therapy (\$232.92)]
PE	5273	Assume 5 additional days in the hospital (\$4103.53), 5 physician inpatient visits (\$286.94), 5 days of therapy with UFH [including 30 000 u/d UFH (\$3.50),* dextrose 5% 500 mL (\$11.80), IV catheter (\$3.96), tubing (\$1.30), pump (\$4.22), phlebotomy (\$17.98), partial thromboplastin time monitoring (\$8.30)], 5 additional office/outpatient visits (\$394.06), and 6 months of warfarin therapy (\$232.92)

DVT indicates deep vein thrombosis; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; HIT, heparin-induced thrombocytopenia; CT, computed tomography; V/Q, ventilation-perfusion

\*Red Book 2001<sup>42</sup>

<sup>†</sup>DRG Guidebook 2001<sup>46</sup>

<sup>‡</sup>RBRVS 2001<sup>45</sup>

<sup>§</sup>Clinical Diagnostic Lab Fee Schedule 2001<sup>44</sup>

<sup>||</sup>Costs provided by Gould (1999)<sup>43</sup> were converted to FY2001 \$ using medical care component of the Consumer Price Index from the Bureau of Labor Statistics.<sup>47</sup>

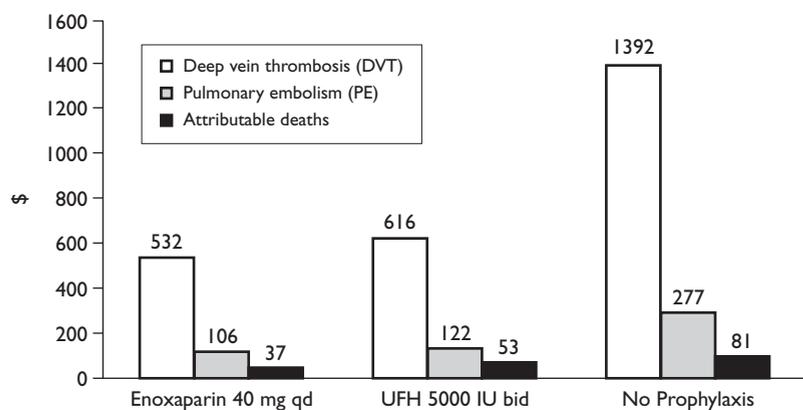
**RESULTS**

**Outcomes of Thromboprophylaxis**

Base-case estimates of the occurrence of DVT, PE, and VTE-related death in a cohort of 10 000 acutely ill gener-

al medical inpatients are presented in **Figure 4**. The risk of each of these outcomes is lowest among patients receiving thromboprophylaxis with enoxaparin and highest among those receiving no prophylaxis. Compared to no thromboprophylaxis, enoxaparin prophylaxis is

**Figure 4.** Estimated Numbers of DVT, PE, and Attributable Deaths Over a 30-day Period Among a Hypothetical Cohort of 10 000 Acutely Ill Medical Inpatients, by Method of Prophylaxis



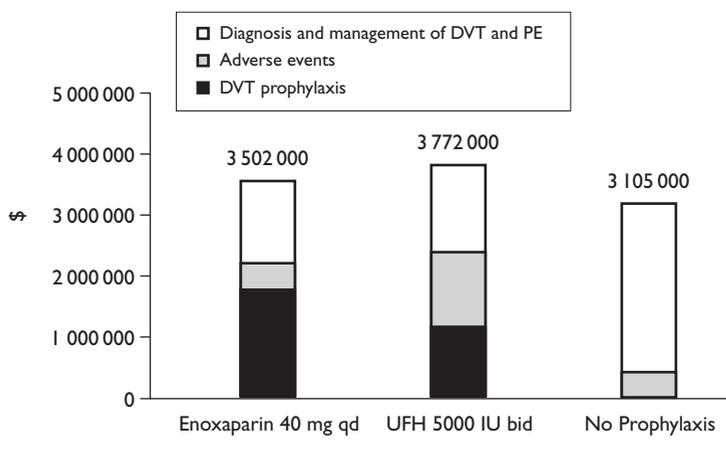
Attributable deaths are those due to pulmonary embolism or to adverse reactions to drugs used in prophylaxis or treatment.

expected to prevent 860 cases of DVT, 171 cases of PE, and 44 deaths, while UFH is expected to prevent 776 cases of DVT, 155 cases of PE, and 28 deaths.

**Costs of Thromboprophylaxis**

The total costs of thromboprophylaxis, adverse events (related to both prophylaxis and treatment of VTE), and diagnosis and management of DVT and PE are presented in **Figure 5**. Patients receiving no thromboprophylaxis had the lowest total costs, fol-

**Figure 5.** Estimated Costs of Venous Thromboembolism Prophylaxis and Treatment Over a 30-day Period Among a Hypothetical Cohort of 10 000 Acutely Ill Medical Inpatients, by Method of Prophylaxis



DVT indicates deep vein thrombosis; PE, pulmonary embolism.

lowed by those receiving enoxaparin and UFH.

**Cost Effectiveness of Thromboprophylaxis**

Results of the incremental analysis comparing a strategy of no prophylaxis with the 2 active prophylactic strategies are presented in **Table 3**. When compared with no prophylaxis, prophylaxis with enoxaparin was the more cost-effective strategy, at a cost of \$9100 per death averted. Unfractionated heparin prophylaxis was dominated by enoxaparin prophylaxis, which was both less costly and more effective in preventing deaths.

**Sensitivity Analyses**

*Subgroup Analysis.* Results for the subgroups of patients with heart failure, respiratory disease, or infectious disease were similar to those for all acutely ill medical patients (**Table 4**). For each subgroup, thromboprophylaxis with enoxaparin dominated that with UFH, and costs per death averted for enoxaparin versus no prophylaxis were even more favorable than in the base case.

*Underlying Risks in Patient Population.* Our findings also were relatively insensitive to variations in the assumed competing risk of death (10% in the base-case analysis). Eliminating the competing risk of death made the results slightly more favorable for enoxaparin. Increasing the underlying risk of death to 20% increased the cost per death averted with enoxaparin versus no prophylaxis by only about \$1000 and did not change the dominance of enoxaparin over UFH. The model was more sensitive to changes in the assumed risk of DVT. When we reduced the risk of DVT in all groups by one half (ie, to 2.8% with enoxaparin, 3.3% with UFH, and 7.1% with no prophylaxis), the cost per death averted for enoxaparin versus no prophylaxis increased to \$56 300, and enoxaparin continued to dominate UFH. In contrast, when we increased the risk of DVT by one half (ie, to 8.3% with enoxaparin, 9.9% with UFH, and 21.3% with no prophylaxis), both active methods of prophylaxis were less costly and more effective than no prophylaxis, with enoxaparin continuing to dominate UFH. When we conducted a similar analysis in which we simultaneously varied the risk of

**Table 3.** Base-case Results for a Hypothetical Cohort of 10 000 Patients

Prophylactic Strategy	Total Cost	Deaths	Incremental Cost	Deaths Averted	Incremental Cost per Death Averted
No prophylaxis	\$3 105 000	1081	—	—	—
Enoxaparin 40 mg qd	\$3 502 000	1037	\$397 000	44	\$9100
UFH 5000 IU bid	\$3 772 000	1053	\$270 000	—	Dominated

UFH indicates unfractionated heparin.

**Table 4.** Results for Hypothetical Subgroups of 10 000 Patients

Prophylactic Strategy	Total Cost	Deaths	Incremental Cost	Deaths Averted	Incremental Cost per Death Averted
<b>Heart Failure</b> (DVT risk: No prophylaxis = 0.146*; Enoxaparin = 0.040*; UFH = 0.048 <sup>†</sup> )					
No prophylaxis	\$3 173 100	1083	—	—	—
Enoxaparin 40 mg qd	\$3 249 700	1029	\$76 600	54	\$1400
UFH 5000 IU bid	\$3 480 200	1043	\$230 500	—	Dominated
<b>Respiratory Disease</b> (DVT risk: No prophylaxis = 0.131*; Enoxaparin = 0.033*; UFH = 0.040 <sup>†</sup> )					
No prophylaxis	\$2 917 500	1075	—	—	—
Enoxaparin 40 mg qd	\$3 131 900	1026	\$214 400	49	\$4300
UFH 5000 IU bid	\$3 350 500	1039	\$218 600	—	Dominated
<b>Infectious Disease</b> (DVT risk: No prophylaxis = 0.155*; Enoxaparin = 0.063*; UFH = 0.076 <sup>†</sup> )					
No prophylaxis	\$3 326 500	1088	—	—	—
Enoxaparin 40 mg qd	\$3 636 800	1042	\$310 300	46	\$6700
UFH 5000 IU bid	\$3 772 000	1053	\$270 000	—	Dominated

DVT indicates deep vein thrombosis; UFH, unfractionated heparin.

\*From Alikhan et al.<sup>48</sup>

<sup>†</sup>Based on relative risk of 0.83 for enoxaparin versus UFH from Mismetti et al.<sup>12</sup>

bleeds with both enoxaparin and UFH from 50% to 150% of the base-case estimates, we found that enoxaparin dominated UFH under both the high-risk and low-risk scenarios, with cost per death averted versus no prophylaxis ranging from about \$5000 assuming lower risk of bleeds to \$14 000 assuming higher risk of bleeds.

*Effectiveness and Side Effects of Enoxaparin vs UFH.* To determine if our results depended on the assumption that enoxaparin had an efficacy advantage over UFH, we assumed equal efficacy (ie, 5.5% probability of DVT) for both methods of prophylaxis. Under this assumption, enoxaparin remained both less costly and more effective than UFH because of the reduced risk of HIT and hemorrhage. Similarly, enoxaparin continued to dominate UFH when equal rates of hemorrhage were assumed for the 2 prophylactic strategies. When both

equal efficacy *and* equal rates of hemorrhage were assumed, we found that UFH was no longer dominated by enoxaparin, and the incremental cost effectiveness of enoxaparin versus UFH was \$43 256 per death averted.

*Other Key Model Parameters.* To examine the sensitivity of our results to changes in drug costs, we calculated the drug price at which enoxaparin would no longer dominate UFH. We found that, up to a per-dose price of \$37.42 for enoxaparin (vs the base-case of \$24.46), the cost per death averted with enoxaparin is lower than with UFH. We also examined the sensitivity of our results to the assumed risk of progression from DVT to PE, both with and without treatment, and the probability of death due to treated or untreated PE. Varying each of these parameters from 50% to 150% of the base-case estimate, we found that our results

were relatively insensitive to these assumptions. For each of these scenarios, thromboprophylaxis with enoxaparin was both less costly and more effective than UFH, and the incremental cost effectiveness of enoxaparin versus no prophylaxis was less than \$21 000 per death averted.

### DISCUSSION

Our analysis highlights a number of important issues related to the choice of thromboprophylactic strategy for medical inpatients. First, the results of our base-case analysis indicate that, given the limitations and assumptions of the model, if the societal value of preventing a VTE-related death among acutely-ill medical patients is at least \$9100, then the use of thromboprophylaxis with LMWH among these patients can be considered cost effective. If each death averted results in a gain of just one quality-adjusted life-year, this marginal cost is well below the often-cited threshold of \$50 000 per quality-adjusted life-year gained.<sup>49</sup> Moreover, despite higher drug acquisition costs, thromboprophylaxis with enoxaparin dominates UFH by being both less costly and more effective.

In sensitivity analyses, enoxaparin remained cost effective in all scenarios examined. The cost-effectiveness advantage of enoxaparin in our model may be seen as due to our assumptions that this drug has greater efficacy as well as a more favorable adverse-event profile than UFH, especially with respect to HIT. But sensitivity analyses showed that even without an efficacy advantage *and* a lower risk of bleeding complications, the incremental cost per death averted with enoxaparin versus UFH is less than \$50 000. This suggests that the reduction in the risk of HIT alone may warrant the use of this LMWH.

Our sensitivity analyses also indicate that, although the incremental cost effectiveness of thromboprophylaxis with a LMWH versus no thromboprophylaxis is somewhat sensitive to changes in the assumed underlying risk of VTE in untreated patients, the incremental cost effectiveness of enoxaparin exceeds \$50 000 only slightly, even when this risk is halved. This suggests that thromboprophylaxis with enoxaparin may be a cost-effective strategy even among medical inpatients at relatively low risk of VTE.

Our findings are qualitatively similar to those of 4 recently published studies that evaluated the cost effectiveness of thromboprophylaxis with LMWH versus placebo in medical patients from Canada,<sup>50</sup> Italy,<sup>51</sup> Spain,<sup>52</sup> and the United States.<sup>53</sup> Our findings are also generally consistent with the published studies in the surgical population. A number of studies have exam-

ined the cost effectiveness of LMWH prophylaxis after total hip replacement surgery and have found it to be cost effective versus both warfarin<sup>54-56</sup> and UFH.<sup>57,58</sup> Studies in the general surgery<sup>59</sup> and trauma<sup>60</sup> populations reported similar results, while a study comparing thromboprophylaxis with LMWH versus UFH after colorectal surgery<sup>61</sup> found UFH to be the more cost-effective strategy. Although most of these studies did not report cost per death averted in US currency, the one study that did<sup>55</sup> reported a cost-effectiveness ratio of \$12 000 per death averted for enoxaparin versus warfarin in total hip replacement surgery, which is in line with our finding of \$9100 per death averted.

Our study is subject to a number of limitations. First, the decision-tree model is necessarily a simplified representation of the disease and treatment process and cannot include all possible strategies and outcomes. Moreover, although our study followed patients for 30 days after admission in order to include thromboembolic events occurring even after hospital discharge, this time period may not capture all of the longer-term consequences of VTE, including post-thrombotic syndrome and increased risk of recurrent DVT. We also recognize that acutely ill medical patients are a heterogeneous group, and estimating cost effectiveness for medical patients as a whole may mask important underlying differences in risks and outcomes between groups.

In addition, we note that probabilities and costs for each of the pathways were estimated by gathering and combining data from a variety of sources. Because, in this population of acutely ill medical patients, no studies have been conducted that compare an LMWH simultaneously to both UFH and placebo, it was necessary to synthesize data on efficacy and adverse events from different studies. In applying the risk-ratio for an LMWH versus UFH from a meta-analysis to the observed risk of DVT with enoxaparin in the MEDENOX trial, we assumed that the risk of DVT with UFH is a constant multiple of the risk with enoxaparin and is independent of the underlying risk of DVT or other patient characteristics. This assumption could not be verified. In addition, because the incidence of adverse events is relatively low for all strategies examined, it was necessary to combine data from a number of studies that used different study designs and populations. The validity and precision of the estimates derived by this process are unknown. We also note that the MEDENOX trial and the trials synthesized in the meta-analysis were conducted on selected groups of medical patients and excluded subgroups such as women of childbearing potential, patients with recent strokes, and those requiring chronic anticoagulation; there-

fore, extrapolation of our finding to these populations may not be appropriate.

The majority of costs used in this analysis were taken from standard sources; the extent to which they reflect the true costs of administering medical care is unknown. In particular, the use of average wholesale prices to estimate drug acquisition costs likely overstates the actual cost of drugs to hospital pharmacies. However, even if the cost of the LMWH used in this analysis was underestimated, sensitivity analyses indicate that an increase of more than 50% in its cost would be required to alter the dominance of enoxaparin over UFH. Finally, this study was conducted from the perspective of the third-party payer and as such does not include such costs of VTE as lost productivity, caregiver time, transportation, and other unreimbursed expenses. Because inclusion of these costs would have increased the costs of thromboembolism, however, the cost-effectiveness argument for enoxaparin thromboprophylaxis would have been strengthened.

In conclusion, when compared with UFH, thromboprophylaxis with enoxaparin is both less costly and more effective. Although prophylaxis with this LMWH in acutely ill medical inpatients is associated with higher medical costs than no thromboprophylaxis, its cost effectiveness compares favorably to other generally accepted medical interventions.<sup>62</sup>

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