

# Cost Utility of Substituting Enoxaparin for Unfractionated Heparin for Prophylaxis of Venous Thrombosis in the Hospitalized Medical Patient

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**BACKGROUND:** Both heparin and enoxaparin are effective for the prevention of venous thromboembolism (VTE) in medical patients. On the basis of price, heparin appears preferable because it is less expensive. However, choosing enoxaparin may have greater cost utility when the outcomes of heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia with thrombosis (HITT) are considered.

**OBJECTIVE:** To determine the cost utility of substituting enoxaparin for heparin from payer and institutional perspectives.

**DESIGN:** A decision analysis model was used. Cost data were based on Medicare reimbursement and the medication and laboratory costs for a multi-institutional healthcare system. Quality-adjusted life years (QALYs) saved by preventing HIT/HITT through the use of enoxaparin were based on published data. Costs are expressed on a per-day basis, and the incremental cost of enoxaparin over that of heparin was used in the calculation of cost/QALY. A sensitivity analysis also was performed.

**SETTING:** Inpatient medicine.

**PATIENTS:** All medical patients for whom VTE prophylaxis was appropriate.

**INTERVENTIONS:** Substitution of enoxaparin for heparin.

**MEASUREMENT:** Cost/QALY.

**RESULTS:** From a payer perspective, using enoxaparin resulted in a decrease in cost of \$28.61 over that of heparin and saved 0.00629 QALYs in the base case, resulting in a savings of \$4550.17/QALY. The sensitivity analysis showed this finding of decreased cost and increased effectiveness to be consistent. From an institutional perspective, the use of heparin generally appeared less costly but was dependent on medication price, length of stay required, and bed utilization.

**CONCLUSIONS:** From a payer and, by extrapolation, a societal perspective, cost-utility analysis supports the use of enoxaparin in place of heparin for the prevention of VTE in medical inpatients. From an institutional perspective, the decision is more complicated, but in most cases, the use of enoxaparin also is supported. *Journal of Hospital Medicine* 2006;1:168–176. © 2006 Society of Hospital Medicine.

**KEYWORDS:** heparin-induced thrombocytopenia, VTE prophylaxis, cost-utility.

Several groups of medical patients at risk for venous thromboembolism (VTE) while hospitalized have been identified. These include patients with certain acute medical illnesses such as acute myocardial infarction, stroke, or chronic obstructive pulmonary disease and those with acute medical illness combined with additional risk factors including advanced age, cancer, obesity, or prior VTE.<sup>1–3</sup>

Heparin-induced thrombocytopenia (HIT) and heparin-in-

**TABLE 1**  
**Efficacy Assumptions**

	Base Case	Range for Sensitivity Analysis
Rate of development of HIT on heparin	2.70%	0.80%–4.90%
Rate of development of HIT on enoxaparin	0.30%	0.09%–0.54%
Rate of progression to HITT	40%	25%–50%
Mortality rate despite treatment, HITT	8%	0%–20%
Assumed extension in length of stay—HIT	1 day	0–5 days
Assumed extension in length of stay—HITT	7 days	5–10 days
Life expectancy (2001)	77.2 years	
Average age of medical inpatient	71.9 years	
QALY adjustment for:		
CHF—severe	0.6	
COPD	0.4	
Cancer	0.9	

duced thrombocytopenia with thrombosis (HITT), a spectrum of disease also known as type 2 HIT, are potentially devastating hematologic consequences of VTE prophylaxis that result from heparin binding to platelet factor IV, leading to IgG antibody-mediated platelet activation.<sup>4–6</sup> These complications manifest along a spectrum from thrombocytopenia alone (HIT) to more severe sequelae that include death, amputation, venous and arterial thrombosis. Unfractionated heparin (UFH) has traditionally been used for VTE prophylaxis in these populations at risk. More recently, evidence has indicated that enoxaparin, a low-molecular-weight heparin, is at least as effective for VTE prophylaxis<sup>1,7</sup> and carries a significantly lower risk for the development of the complications of HIT and HITT. Despite the superior side-effect profile of enoxaparin, many institutions encourage the use of heparin for DVT prophylaxis because of its lower price. However, when the costs of treating these complications are considered, using unfractionated heparin may actually be more costly.

Two studies of the cost effectiveness of heparin compared with enoxaparin when used for VTE prophylaxis in medical inpatients have recently been published.<sup>8,9</sup> However, one of these studies focused only on pharmacy-related costs and did not consider patient-related outcomes, and the other was published by a for-profit research company. Studies of treatment with enoxaparin versus UFH in other medical settings, including non-Q-wave myocardial infarction<sup>10</sup> and treatment of acute deep-vein thrombosis,<sup>11</sup> suggest that enoxaparin is more cost effective. Studies of prophylaxis of surgical patients have been contradictory. Data suggest that in orthopedic patients the use of enoxaparin is more

cost effective for both short- and long-term VTE prophylaxis,<sup>12–14</sup> but low-dose heparin appeared more cost effective for patients undergoing colorectal surgery, in large part because of an assumption of a smaller risk of bleeding.<sup>15</sup>

The purpose of this analysis was to determine the cost utility of heparin compared with enoxaparin for VTE prophylaxis for medical inpatients at risk. In such an analysis, it is important to consider the possibly different meanings that entities may attach to *cost utility* and *effectiveness* according to their different roles in the health care system. Individual institutions pay inpatient medication costs, but they often do not directly bear the costs of complications of treatment and may actually receive reimbursements for them. In contrast, payers must provide that reimbursement. For this reason, costs were analyzed from 2 perspectives, that of a payer (Medicare) and that of a health care system or institution.

## METHODS

This protocol was declared exempt by the Institutional Review Board at the University of Texas Health Science Center at San Antonio.

### Estimates of Effectiveness

Estimates of effectiveness include those related both to efficacy in preventing VTE, and those related to adverse drug events. They are summarized in Table 1.

Assumptions about the efficacy of heparin and enoxaparin when used for VTE prophylaxis were based on the following published data. The rate of development of VTE reported in the Medenox trial, 5.5%,<sup>1</sup> is consistent with rates reported for patients

receiving heparin (2%-13%).<sup>16-18</sup> More recently, the PRINCE study demonstrated that enoxaparin was at least as effective as heparin in patients with severe heart failure or respiratory disease and was more effective in the former group of patients.<sup>7</sup> Finally, data from patients with acute stroke indicated that low-molecular-weight heparins are at least as effective as heparin for this indication.<sup>19,20</sup> Equal efficacy was assumed for this analysis for several reasons, primarily to avoid the creation or amplification of errors through the introduction of more assumptions about the proportion of patients with specific diagnoses and about the magnitude and range of differences in efficacy. Only one study has examined the relative efficacy in patients with congestive heart failure, and not all the results of studies in stroke patients pointed to enoxaparin having improved efficacy. Therefore, making valid assumptions about the magnitude of the difference between the drugs on the basis of the available evidence may not be possible.

It was also assumed that aside from HIT and HITT, the 2 drugs had the same rates of adverse events, including bleeding complications, in this patient population.<sup>1</sup>

A Medline search combining MeSH terms *thrombocytopenia* and *heparin* was done to find the appropriate incidence of HIT and HITT. The resulting group was further limited in 3 separate searches using the terms *prophylaxis* (keyword), *incidence* (MeSH term), and *thromboembolism or venous thrombosis* (MeSH terms). Heparin-induced thrombocytopenia was searched for as a keyword and combined with the MeSH term *prophylaxis* in a separate search. Finally, reference lists were searched to find additional articles.

The range of reported rates of development of HIT among patients receiving heparin was wide. In part, this is related to the different subgroups of patients studied and to the inclusion of patients receiving both prophylaxis and treatment doses of heparin. The one study that looked specifically at medical inpatients included patients receiving treatment-dose heparin. The rate of HIT in this study was 0.8%.<sup>21</sup> A study of both prophylactic and therapeutic use in neurologic patients reported a rate of 2.5%.<sup>22</sup> Studies specific to VTE prophylaxis in surgical patients reported a range of 0.8%-4.9%.<sup>23-26</sup> Based on these results, a rate of 2.7%, the median of the reported ranges, was used for the base case, and 0.8% and 4.9% were used for sensitivity analysis.

The reported rates of progression to thrombosis for patients with HIT ranged from 25 to more than 50%.<sup>21,27,28</sup> A median rate of 40% was used for the base case, and 25% and 50% were used for sensitivity analysis. It was assumed that 0.3% of patients receiving enoxaparin developed HIT, 1/9 as frequently as those receiving heparin,<sup>24,25,29</sup> but that the same percentage of those with HIT would develop thrombosis.

Mortality secondary to thrombosis in patients with untreated HIT has been reported to be 4%-5%.<sup>30,31</sup> All-cause mortality in untreated patients with HITT has been reported to be as high as >20%,<sup>31,32</sup> but in treated patients it has been reported as 8%.<sup>30</sup> A mortality rate of 8% for HITT despite treatment was assumed with a range in the sensitivity analysis from 0% to 20%.

Life expectancy data were obtained from the National Center for Health Statistics, and the average age of medical inpatients potentially eligible for DVT prophylaxis was calculated from this data. The catalog of preference scores was obtained from the Cost Effectiveness Analysis Registry at the Harvard Center for Risk Analysis.<sup>33</sup> These preference scores adjust the quality of a year of life for chronic diseases and provide a more accurate assessment of quality-adjusted life years.

It was assumed that patients with HIT alone would be treated with argatroban, consistent with evidence that this is superior to withdrawal of heparin alone in patients with HIT.<sup>28</sup> Using other agents such as lepirudin for the treatment of HIT was not considered in this analysis because there is no data on which to base their efficacy in patients with HIT.

For treatment of patients with HITT, again only the use of argatroban was considered. Though other agents are as efficacious in treating HITT, they are also more expensive. Therefore, using argatroban allowed for a more conservative estimate.

Platelet counts typically fall after 5 days of heparin administration in patients developing HIT<sup>34</sup> and typically recover within 3-5 days of initiation of treatment.<sup>4,29</sup> In the past, patients may not have been kept in the hospital for resolution of their platelet count. However, with evidence that HIT should be aggressively treated, patients with HIT will likely have a longer length of stay. A study of treatment of HIT reported a mean time on argatroban of 5-7 days.<sup>23</sup> This is greater than the average length of stay for medical diagnosis, which is 4-5 days.<sup>35</sup> Therefore, an additional length of stay of 1

**TABLE 2**  
**Cost Assumptions**

	Medicare-related		Institution-related	
	Base case	Range	Base case	Range
Additional reimbursement for HIT (if considered a complicating condition)	\$ 765.06	\$ 0.00	\$ 765.06	\$0.00
Additional reimbursement for HITT (if coagulation disorder DRG used)	\$1135.56	\$ 0.00	\$1135.56	\$0.00
Primary provider visit (99232)	\$ 54.89	\$33.00–\$ 78.04	n/a	
Consultant initial visit (99254)	\$ 140.39	\$35.84–\$193.03	n/a	
Consultant follow-up (99263)	\$ 44.80	\$22.40–\$ 66.09	n/a	
<i>Medication (per day)</i>				
Heparin	n/a		\$ 4.00	
Enoxaparin	n/a		\$ 84.00	
Argatroban	n/a		\$ 150.00	
Coumadin	n/a		\$ 0.50	
<i>Laboratory tests (per test)</i>				
Complete blood count	n/a		\$ 2.14	
Prothrombin time/partial thromboplastin time	n/a		\$ 9.85	
Opportunity cost per additional day of hospitalization (if hospital at capacity)	n/a		\$1096.72	

day was assumed for patients given a diagnosis of HIT, with a range of 0–5 days used for the sensitivity analysis. An additional length of stay totaling 7 days was assumed for those with thrombosis, based on patients requiring 7 days of argatroban therapy for treatment of HITT in a recent study.<sup>28</sup>

### Estimates of Costs

Costs were analyzed from institutional and Medicare perspectives. Only direct medical expenditures related to hospitalization were considered; indirect patient costs resulting from the sequelae of HITT, while potentially severe, were not included. An incremental analysis was performed to express the increase in resources used when a person develops HIT/T, with the final result expressed as a daily cost of each medication. Cost assumptions are summarized in Table 2.

### Medicare Related

Diagnosis-related group (DRG) reimbursement to institutions and physicians were considered the only payer-related costs. These were based on the 2005 Medicare reimbursement.<sup>36</sup> Costs related to laboratory, medication, or other diagnostic studies were assumed to be covered by the DRG payment and not to be billed separately.

The average Medicare reimbursement to institutions for all diagnosis-related groups is the national standard number, or \$4971.81. To determine the additional potential charges resulting from the development of HIT, it was considered a compli-

cating condition. The average adjustment factor for complicating conditions of medical diagnoses is .1539, leading to an increase in charges of \$765.06. No additional adjustments for geographic location were made. Sensitivity analysis was performed with no additional reimbursement for HIT as a complicating condition.

To quantify additional charges related to caring for patients with HITT, we used the amount of additional charges for the coagulation disorder DRG (#397) above those of the average reimbursement. This amount is \$1135.56, the difference between the higher charge of \$6107.37 for this DRG, and the national standard number. Sensitivity analysis with no additional charges was performed.

Physician charges used were based on the 2004 Medicare reimbursement.<sup>36</sup> It was assumed that each patient with HIT would have a daily visit of moderate complexity (CPT 99232), which carries a reimbursement rate of \$54.89. Patients with thrombotic complications were assumed to also have a hematology consult consisting of one initial visit and one follow-up, both of midlevel complexity (CPTs 99253 and 99262). The reimbursement rates for these visits are \$97.45 and \$44.80. Sensitivity analysis using both lower- and higher-level visits was performed (Table 2).

Based on the above DRG and physician reimbursements, the total cost to Medicare of treating a patient with HIT is \$820.05 and of treating a patient with HITT is \$1749.98. For the situation in which a

patient with HIT also developed HITT, only the cost of reimbursement for HITT was modeled.

### *Hospital-Related*

To calculate the benefit or cost to an institution, 2 scenarios were modeled. In the first scenario, only the DRG-related revenues collected and the costs of caring for patients with HIT/T were considered. The revenues used are described above. The cost of medications at a multi-institutional health care system (MIHCS) was obtained from the pharmacy and used in this analysis. This system is composed of a network of urban and suburban acute care facilities with academic affiliations with 2 universities. Costs are representative of the entire system. The cost of heparin is \$2.00 per unit dose; daily cost for b.i.d. prophylaxis is \$4.00. The cost of one daily dose of enoxaparin is \$84.00. One unit (50 mg) of argatroban costs \$50.00. For a 70-kg man at a standard dosing rate of 2  $\mu\text{g}/\text{kg}$  per minute, the daily cost would be approximately \$150.00. The daily cost of coumadin was estimated at \$0.50 regardless of the dose. The cost of laboratory tests within the MIHCS is \$2.14 per complete blood count and \$9.85 for each PT/PTT.

Other costs, such as those related to the additional time spent by nursing and pharmacy staff in the mixing and administration of argatroban or caring for patients with HIT and HITT were not included in this analysis, as it was believed that they would have no impact on actual staffing levels and would not lead to a tangible or easily quantifiable increase in expenditures.

In the second scenario, the potential loss of income from additional days of hospitalization for HIT and HITT was considered. An institution could potentially lose money if a patient with HIT or HITT stayed longer than the number of days that is economically attractive given the DRG reimbursement. In this scenario, a longer length of stay of a patient with HIT or HITT could lead to the bed not being used by other patients for whom the hospital could be collecting revenue. This would only be applicable with high occupancy rates. The average revenue per day that a hospital could receive for a patient was calculated by dividing the average reimbursement, \$4971.81, by the average length of stay for medical inpatients, 4.5 days. This amount is \$1096.72. The amount of additional reimbursement for a complicating condition, \$754.06, then covers 0.7 days of additional hospitalization. As described above, the average additional reimbursement for

using the coagulation disorder DRG for patients with HITT, instead of using the DRG for which they were otherwise admitted, was \$1135.56. This would cover an additional 1.04 days of hospitalization. If the hospital stay of patients with HIT/T were to be longer, an amount computed as \$1096.72 multiplied by the number of additional days of hospitalization was considered a loss of income borne by the hospital.

### **Sensitivity Analysis**

Sensitivity analysis was performed to ensure the validity of results over a range of values and to assess the effect of medication prices on our findings. The analysis used these parameters, both alone and in combination: rate of development of HIT, rate of development on enoxaparin compared with on heparin, percentage of those with HIT who developed thrombosis, mortality related to HITT, length of stay of patients with both HIT and HITT, reimbursement rates, and costs of medication.

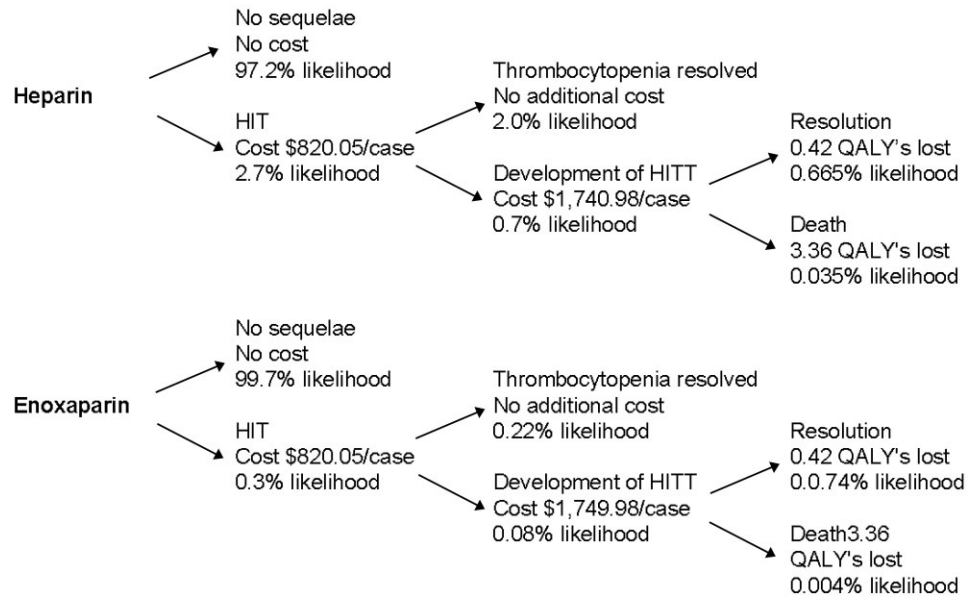
### **RESULTS**

The decision tree used for the base-case analysis is shown in Figure 1. The gain in quality-adjusted life years (QALYs) for medical patients who used enoxaparin rather than heparin for VTE prophylaxis was 0.00629 (approximately 55 hours). This was based on the decrease in HITT-related premature death resulting from the use of enoxaparin. From a payer perspective, the daily cost of enoxaparin is \$3.58, compared with \$32.18 for heparin. The difference is a savings of \$28.61, leading to a savings/QALY of \$4550.17. Therefore, the use of enoxaparin is both more effective and less costly.

Sensitivity analysis showed that from a payer perspective, enoxaparin remained both less costly and more effective in all cases. The factors that had the largest impact on cost/QALY were incidence of HIT and rate of thrombosis among those with HIT. Decreasing length of stay to 0 for patients with HIT, decreasing reimbursement to \$0 for both HIT and HITT, and billing at a high or low level did not change the general finding. Decreasing the cost of enoxaparin or heparin also did not affect these findings. The results of the sensitivity analysis are summarized in Table 3.

From an institutional perspective, the effect of considering the costs of HIT and HITT did not necessarily make enoxaparin a more attractive choice. When potential reimbursement for drug-related complications was considered, an institu-





**FIGURE 1.** Decision tree for base-case analysis.

**TABLE 3**  
Payer Perspective: Savings, QALYs Gained for Base Case and Sensitivity Analysis

	Enoxaparin (cost/day)	Heparin (cost/day)	QALYs saved	Savings/QALY
<b>Base case</b>	<b>\$3.58</b>	<b>\$32.18</b>	<b>0.00629</b>	<b>\$4550.17</b>
<i>Sensitivity analysis</i>				
Incidence of HIT	\$1.06–\$6.49	\$ 9.54–\$58.11	0.00186–0.01141	\$4550.17
Progression of HIT to HITT	\$3.12–\$3.77	\$28.05–\$33.95	0.00393–0.00786	\$6344.53–\$3840.30
Level of physician visit billed	\$3.23–\$3.81	\$28.45–\$34.27	0.00629	\$4021.85–\$4844.35
HIT length of stay	\$3.48–\$3.64	\$31.30–\$32.78	0.00629	\$4424.46–\$4633.98
No reimbursement for HIT	\$2.13	\$19.20	0.00629	\$2713.90
No reimbursement for HITT	\$0.77	\$ 6.93	0.00629	\$ 980.05

tion actually make \$7.27/day by choosing heparin, whereas the cost of enoxaparin decreases only minimally from \$84.00 to \$82.75/day (Table 4). Factoring opportunity costs into the analysis showed that an institution does not make money by using heparin, but heparin still costs less on a daily basis. This finding changes only at rates of HIT over 4%.

Sensitivity analyses of institutional costs are summarized in Table 4. These analyses demonstrated that potential increases in length of stay for patients with HIT or HITT could make heparin less attractive when opportunity costs to the hospital are considered. If the additional length of stay for patients with HIT increased to greater than 1.75 days or the additional length of stay for those with HITT increased to more than 9 days, heparin becomes a less attractive choice. Loss of reimburse-

ment for HIT or HITT alone does not make enoxaparin less costly than heparin.

Sensitivity analysis also demonstrated that variation in the price of enoxaparin could potentially make heparin less attractive. If the price of heparin were held constant at \$4.00/day, enoxaparin would become less costly at a price of \$37.00. If the price of heparin were to decrease to as low as \$0.50/day, the price at which enoxaparin would be more attractive decreased to \$33.00. These prices are only applicable when the opportunity costs of having occupied beds are considered—that is, only when an institution is operating at full capacity. When this is not the case, enoxaparin would have to cost less than \$1.00 to be more financially attractive than heparin. In practical terms, unless a hospital is at full capacity and needs hospital beds for other

**TABLE 4**  
**Institutional Costs: Base Case and Sensitivity Analysis**

	Heparin		Enoxaparin	
	Drug cost alone	Drug cost + cost of increased LOS	Drug cost alone	Drug cost + cost of increased LOS
<b>Base case</b>	<b>(\$7.27)</b>	<b>\$72.33</b>	<b>\$82.75</b>	<b>\$91.59</b>
<i>Sensitivity Analysis</i>				
Incidence of HIT	\$ 0.66–(\$16.45)	\$24.25–\$128.01	\$83.63–\$81.75	\$86.25–\$ 97.18
Length of stay HIT	(\$ 7.27)	\$42.72–\$190.78	\$82.75	\$88.30–\$104.75
Length of stay HITT	(\$ 7.27)	\$48.64–\$101.57	\$82.75	\$88.96–\$ 95.54
Drug costs below which enoxaparin is more attractive	\$ 0.50 – \$ 4.00	\$ 0.50–\$ 4.00	\$33.00–\$37.00	< \$1.00

patients, the cost of enoxaparin would have to be less than \$1 for an institution to choose it instead of heparin.

## DISCUSSION

This study demonstrates that from a payer perspective, there is greater cost utility in the use of enoxaparin in place of heparin for the prevention of venous thromboembolism in at-risk medical patients. This benefit is based on a single advantage of enoxaparin: its decreased tendency to cause HIT/T. Despite the simplicity of this assumption, it is well supported by published data. Sensitivity analyses supported the finding that enoxaparin was a superior choice in all scenarios modeled. This payer data can be extrapolated to a societal level because the costs used were based on Medicare reimbursements.

The benefit of using enoxaparin when expressed in an absolute number of quality-adjusted life years was small, approximately 55 hours. This reflects that although the effects of HIT and HITT are potentially devastating, they occur infrequently. However, our calculation was conservative in several respects. We calculated the highest possible average age for a medical inpatient based on the available statistics. This was done to ensure that we were not overestimating the number of QALYs saved by preventing death secondary to HITT. We also considered only 2 outcomes of HITT: death and recovery. This underestimates the significant potential thrombotic complications, notably amputation or other loss of function, which would increase the number of QALYs saved by using enoxaparin. The inclusion of these complications would only strengthen this finding. Finally, we assumed equal efficacy for heparin and enoxaparin. The in-

clusion of superior efficacy of enoxaparin in subpopulations of medical inpatients would again only strengthen this finding.

Apart from the price of the medication, the incidence of HIT had the largest impact on costs and QALYs saved in the sensitivity analysis. Studies specific to VTE prophylaxis in medical inpatients could better define the incidence of HIT/T in this population, but this would not change our overall finding.

From an institutional perspective, the choice of heparin or enoxaparin is more complicated. In most but not all scenarios, the use of heparin appears to be more financially attractive. The prices of enoxaparin and heparin, the additional length of stay required to care for patients with HIT and HITT, and the percentage of total beds occupied all affect this decision. Several pieces of cost data, specifically those related to medication and laboratory testing, were specific to an MIHCS health care system, the type considered in the analysis and could potentially limit the applicability of this study to other institutions. However, the sensitivity analysis demonstrated that the cost of enoxaparin would have to be at least 60% lower, below \$33/day, before affecting our conclusion, and then only if an institution were at full capacity. Thus, we expect that our results are generally applicable.

The potential limitations of this study are related to the assumptions required. However, our efficacy assumptions were conservatively based on published data. It is possible that a decrease in the rate of thrombosis if all cases of HIT were treated with argatroban could affect our findings. However, in the study by Lewis et al., the complication rate for those with HIT in the treatment group was 28% (versus 38.8% in the untreated

group), consistent with rates used in our sensitivity analysis. DRG and physician reimbursements are based on published Medicare data. The greatest variation is likely to be in drug cost, as different institutions may negotiate lower prices. From a payer perspective, drug costs do not affect the conclusions; from an institutional perspective, drug cost may make the choice a complicated one. One factor not included in our analysis that may affect this decision is the possible impact of legal action on the medications institutions choose for VTE prophylaxis. Because the potential consequences of HITT can be so devastating, an institution could have difficulty defending the choice of heparin when an equally effective alternative with fewer adverse events was available. A settlement of \$1 million could potentially pay for prophylaxis with enoxaparin for at least 2500 patients.

This analysis has highlighted one of the unfortunate paradoxes caused by the different, potentially competing incentives in our health care system. Payers and institutions often face different financial incentives. From a hospital's perspective, it may cost less to use an intervention that can potentially cause a greater number of complications and higher payer costs. We believe that for VTE prophylaxis for medical inpatients, improved patient outcomes coupled with decreased payer/societal costs argue strongly for the use of enoxaparin over unfractionated heparin and outweigh any institutional benefits.

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