

A PROBABILISTIC COST-EFFECTIVENESS ANALYSIS OF ENOXAPARIN VERSUS UNFRACTIONATED HEPARIN FOR THE PROPHYLAXIS OF DEEP-VEIN THROMBOSIS FOLLOWING MAJOR TRAUMA

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ABSTRACT

Background

In the absence of major contraindications, treatment guidelines recommend that, following a major traumatic event, all patients receive low molecular weight heparin (e.g. enoxaparin) as thromboprophylaxis for the prevention of deep vein thrombosis (DVT).

Objective

To estimate the incremental cost-effectiveness of enoxaparin versus low dose unfractionated heparin (UH) for the prophylaxis of DVT following major trauma.

Methods

Using probabilistic decision-analytic modeling, we estimated the incremental cost-effectiveness of enoxaparin versus unfractionated heparin for the prophylaxis of DVT following moderate to severe trauma (injury severity score ≥ 9) over a life-time horizon from the perspective of the health care payer. Cost effectiveness was calculated based on both the incremental cost (ΔC) per DVT averted and the ΔC per life year gained (LYG).

Results

The incremental cost of enoxaparin relative to UH was C\$90, and the incremental effectiveness was 0.085 DVTs averted and -0.13 LYG. This resulted in an incremental cost-effectiveness ratio of C\$1,059 per DVT averted, and the conclusion that UH is the dominant strategy in terms of LYG. In addition to the probabilistic analysis, one-way and two-way sensitivity analysis revealed that the model was most sensitive to variation in the discount rate (3% - 7%), but that UH remained the dominant strategy in terms of life years independent of the parameter estimates.

Conclusions

Although enoxaparin appears to be a cost-effective alternative when considering the intermediate endpoint of DVTs averted, it may be dominated by UH in terms of LYG due to the higher incidence of major bleeds in patients receiving enoxaparin versus UH.

Key Words: *Enoxaparin, heparin, thromboembolism, trauma*

Venous thromboembolism is a common and potentially life-threatening complication of major trauma. In a prospective study, Geerts et al.

used contrast venography to evaluate 349 patients following major trauma (injury severity score (ISS) ≥ 9) and found that 58% had a detectable

deep vein thrombosis (DVT), 18% of which were proximal, putting them at high risk of embolization and progression to pulmonary embolism (PE), the third most common cause of mortality in trauma patients.¹ It has been estimated that without DVT prophylaxis, up to 22% of trauma patients will develop a PE, one-third of which are fatal in patients that survive the first 24 hours post-trauma.¹⁻³

Due to the underlying traumatic injury and the potential need for surgery, there has been a historical concern over potential bleeding-related complications associated with anticoagulant DVT prophylaxis in trauma patients. A randomized controlled trial (RCT) comparing enoxaparin to unfractionated heparin (UH) for the prophylaxis of DVT following major trauma concluded that enoxaparin was more effective ($p=0.012$) and did not result in any increase risk of major bleeding ($p=0.12$) despite the occurrence of 5/136 major bleeds in the enoxaparin group versus 1/129 major bleeds in the patients receiving UH. Although this study was published in 1996, enoxaparin remains the agent of choice in this population at many institutions.⁴

In addition to evidence of comparative safety and efficacy of new or alternative therapeutic strategies, health care payers and institutions are increasingly requiring evidence of cost-effectiveness to ensure the most efficient allocation of limited health care resources. Because enoxaparin and UH are similar in terms of route of administration, dosing frequency, monitoring requirements, and are now very similar in terms of acquisition costs (C\$12.08 versus \$4.14, respectively); differences in outcomes and their associated costs have therefore become more important.

The objective of this study was to use all available data to estimate the incremental cost-effectiveness of enoxaparin versus low-dose UH for the prophylaxis of DVT following major trauma in patients with a trauma score of ≥ 9 , from the perspective of the health care payer over a life-time time horizon. We used a framework of probabilistic decision-analytic modeling to incorporate the second order uncertainty of model parameters into the analysis, and to combine cost and effectiveness data to estimate the incremental cost effectiveness ratio (ICER) in terms of both

incremental cost (ΔC) per DVT averted and the ΔC per life year gained (LYG).

METHODS

Evaluation of Clinical Efficacy

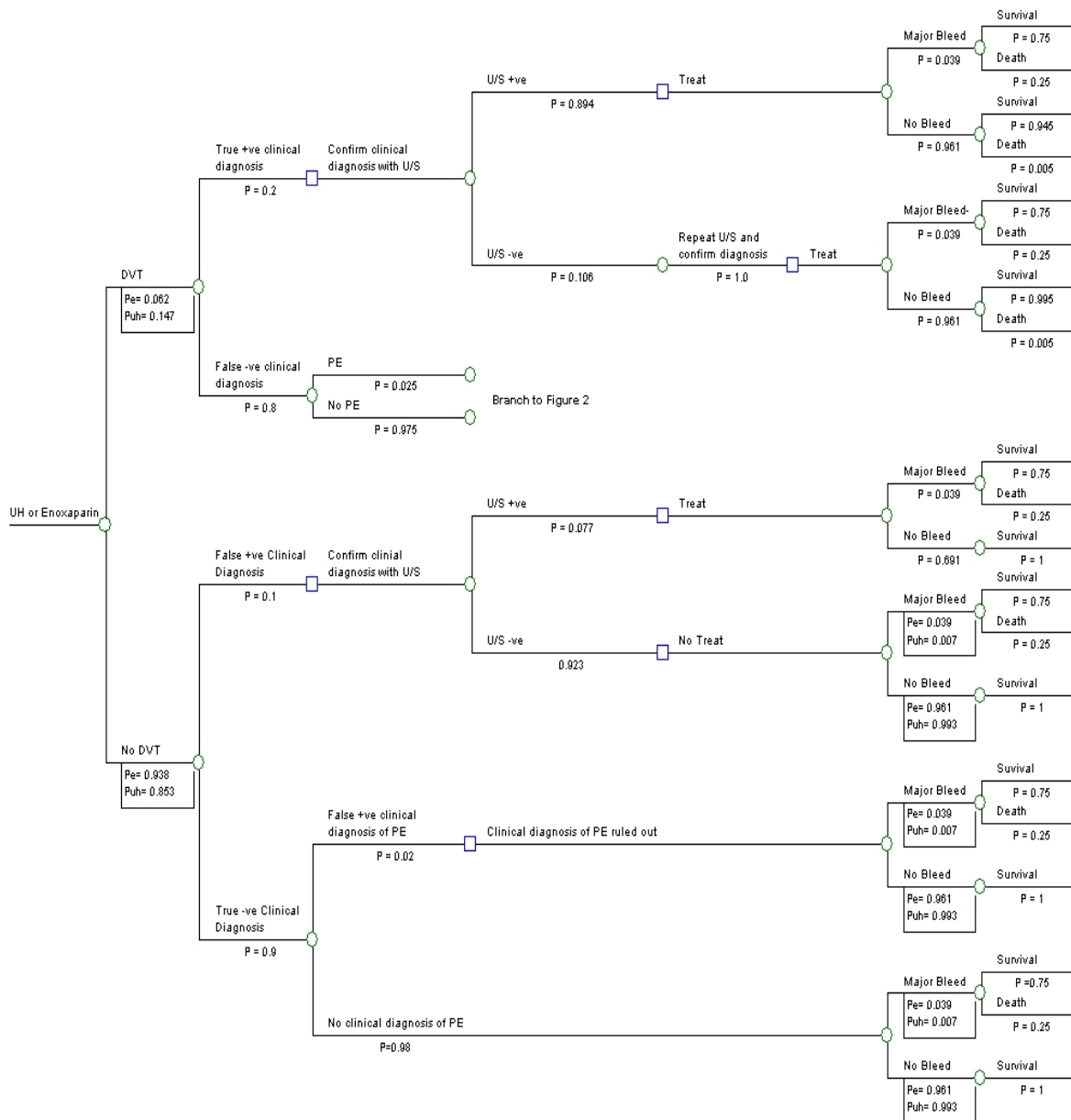
To determine the safety and efficacy of enoxaparin and UH for DVT prophylaxis in trauma patients, we searched the English language literature using Medline and EMBASE to identify all clinical trials published up to January 2004. For inclusion, a study had to be a RCT evaluating enoxaparin or UH either head to head, or to any other prophylactic agent, in patients experiencing major trauma, and include data on both efficacy (prevention of DVT) and risk (i.e. major bleeding).

Decision Analysis

Although venography is the gold standard for DVT detection, there are data demonstrating that many DVTs do not produce symptoms or clinical sequelae and therefore go undetected. Furthermore, most RCTs of DVT prophylaxis use the intermediate endpoint of DVTs averted, whereas from an effectiveness perspective, the more important outcomes are the prevention of pulmonary embolism (PE) and deaths secondary to either PE or DVT prophylaxis or treatment related major bleeds. Therefore, in consultation with clinical experts in DVT management in the critical care setting, we developed a probabilistic decision analytic model for post-trauma DVT prophylaxis, which includes all intermediate and final endpoints.

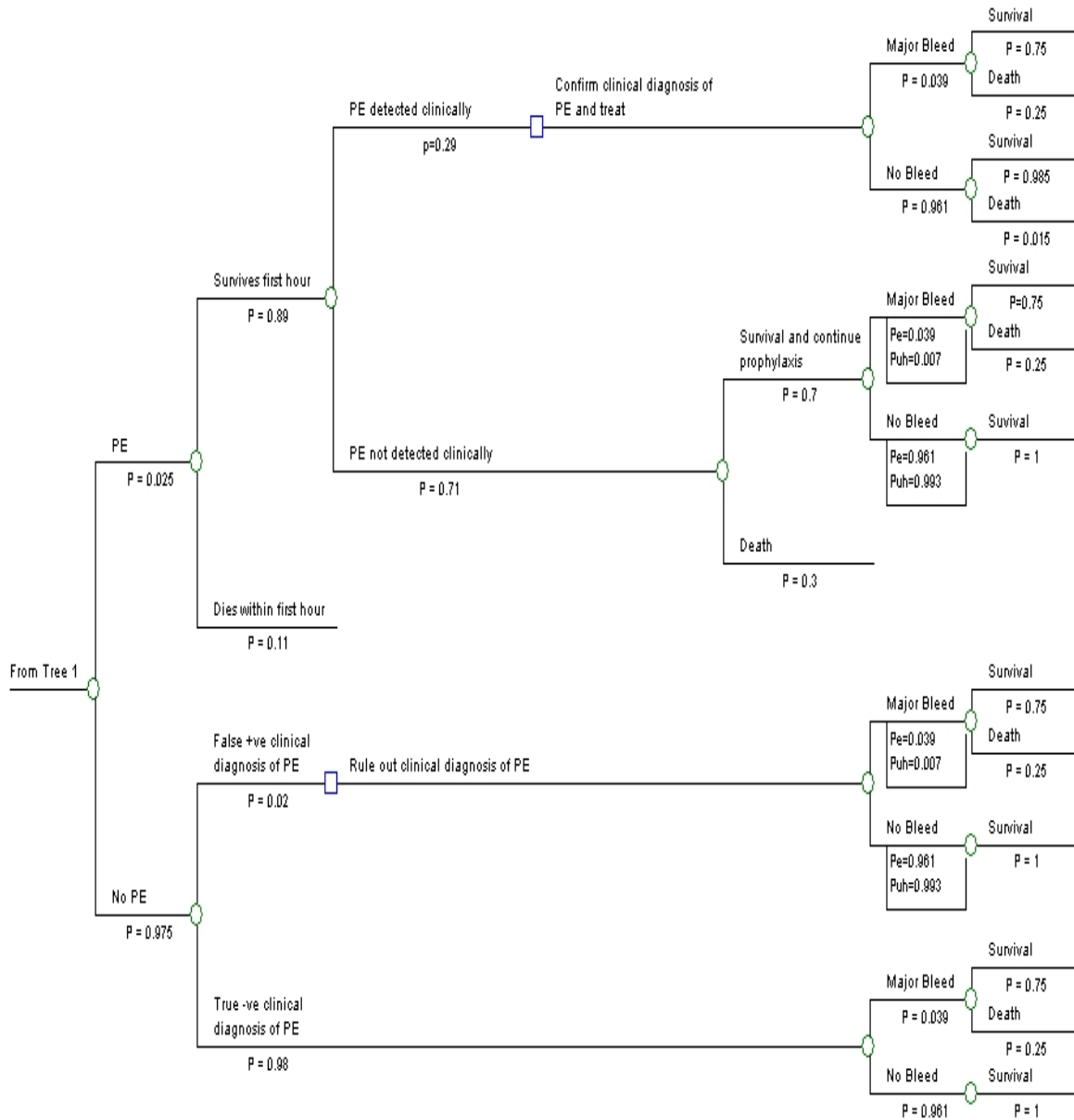
The first branch of Figure 1 incorporates the probability of developing a DVT derived from the clinical trials, followed by four branches illustrating the management of patients depending upon whether they have a DVT and receive either a true positive (branch 1) or false negative (branch 2) diagnosis, or they do not have a DVT and receive a false positive (branch 3) or true negative clinical diagnosis (branch 4). The sub-tree for patients developing a PE is illustrated in Figure 2.

FIG. 1 Main Decision Tree for Diagnosing and Managing Deep-Vein Thrombosis (DVT) Following Major Trauma



Squares (□) denote choice nodes and circles (○) denote chance nodes. Branches from chance nodes have associated probabilities that sum to 1 for each node. Probabilities specific to enoxaparin and unfractionated heparin are denoted by P_e and P_{uh} , respectively. PE = pulmonary embolism.

FIG. 2 Pulmonary Embolism Sub-tree



Squares (□) denote choice nodes and circles (○) denote chance nodes. Branches from chance nodes have associated probabilities that sum to 1 for each node. Probabilities specific to enoxaparin and unfractionated heparin are denoted by P_e and P_{uh} , respectively. PE = pulmonary embolism.

Clinical and Diagnostic Probabilities

Because proximal DVTs are the most clinically important in terms of the potential for embolizing and causing a PE, we focused our model on the rates of proximal DVTs only. In addition to the

rates of DVT and major bleeding from the clinical trials, additional data on the clinical and diagnostic probabilities were derived from available literature (Table 1).

TABLE 1 Event Probabilities, Accuracy of Diagnostic Testing and α and β Parameters of the Beta-Distribution

Description	Probability	Beta-Distribution Parameters		Source
		α	β	
Proximal DVT in UH group	0.147	1	128	25
Proximal DVT in enoxaparin group	0.062	5	131	25
PE	0.025	33	1283	3, 17, 18
Major bleed during treatment of DVT with UH	0.040	20	80	9, 10, 12
Major bleed during prophylaxis – enoxaparin	0.039	90	10	25
Major bleed during prophylaxis – UH	0.007	1	135	25
Death due to Major Bleed	0.250	2	6	9, 12
Death due to DVT treatment failure*	0.005	5	994	16
Death due to PE treatment failure*	0.015	15	984	16
PE detected Clinically	0.290	29	71	3, 19
False positive clinical diagnosis of PE*	0.020	2	98	19
Survives first hour following PE	0.890	132	1068	19, 20, 34, 35 EO
Death due to PE	0.300	7	14	3, 19, 20
Sensitivity of Clinical Diagnosis of DVT	0.200	20	80	19, 36, 37
Specificity of Clinical Diagnosis of DVT	0.900	90	10	9, 19
Sensitivity of B-mode ultrasonography	0.89	101	12	5, 6, 38
Specificity of B-mode ultrasonography	0.95	2	24	7

*Specific α and β values not available from the literature, therefore values assigned based on the probability and varied across other potential values in sensitivity analysis. PE = pulmonary embolism; DVT = deep vein thrombosis; UH = unfractionated heparin; EO = expert opinion

Following a positive clinical diagnosis of DVT, we assumed that the diagnosis would be confirmed or ruled out using B-mode ultrasonography (U/S; sensitivity 0.89, specificity 0.90),⁵⁻⁷ and that all unconfirmed true positive clinical diagnoses would be confirmed with a second ultrasound after three days (sensitivity 1.0). We also assumed that every PE arises from

an undetected DVT and that all clinically suspected PE's would be confirmed using a 2-view portable chest x-ray and spiral computer tomogram (CT).

Due to the absence of events in the clinical trial, treatment-related bleeding rate and bleed-related mortality were derived from the literature. Approximately 4.0% of patients who develop a

DVT and receive treatment will develop a major bleed secondary to treatment.⁸⁻¹⁰ Although in RCTs of UH therapy for DVT the overall mortality rate due to major bleeding was only 1 in 1400 patients treated, the case fatality rate was 25%.^{8,9,11-15} Despite appropriate diagnosis and treatment, there remains approximately a 0.05% and 1.5% chance of dying due to the failure of treatment of a DVT and PE, respectively.¹⁶ The conditional probability of developing a PE given that a DVT occurred was estimated to be 0.025,^{3,17,18} with a subsequent probability of death due to a PE in the absence of a diagnosis and treatment of approximately 0.30.^{3,19,20}

Costs of Prophylaxis, Diagnosis and Treatment

All costs of prophylaxis, diagnosis, and treatment are summarized in Table 2 (2003 Canadian dollars). The cost of DVT prophylaxis was based

on the drug acquisition cost of 5,000 units of UH (\$4.24) and 30mg of enoxaparin (\$12.08), which were obtained from St. Joseph's Healthcare in Hamilton, ON, Canada. The cost of administration and procurement were assumed to be the same for both prophylactic strategies, and were estimated based on expert opinion of nursing time involved and the mean hourly nursing wage for a general duty nurse obtained from the 2003 Ontario Nurses Union collective bargaining agreement (inflated by 20% to account for provision of benefits). We assumed that all patients requiring DVT treatment would receive intravenous UH at a mean daily dose of 30,000U/day (\$6.60) with twice daily measurement of the activated partial thromboplastin time (aPTT) (\$7.94/test), and nursing time would entail approximately 20 minutes per day (\$10.80).

TABLE 2 Costs and Length of Stay Included in the Base Case Analysis

Treatment/Intervention	Unit cost	
Enoxaparin for Prophylaxis (per day)	\$12.08	
Unfractionated Heparin for Prophylaxis (per day)	\$4.24	
Ultrasound	\$196.58	
ICU day	\$944.16	
Hospital Day	\$550.32	
Spiral CT	\$159.13	
2 views portable x-ray	\$51.34	
Length of Stay	Mean LOS (Std. Dev)*	
	ICU	Medical Ward
No DVT / no complications	8.2 (19.9)	6.6 (9.2)
No DVT / major bleed due to prophylaxis	15.7 (19.0)	13.9 (17.2)
DVT / no complications	16.1(21.7)	27.7 (21.0)
DVT / major bleed due to treatment	18.5 (11.6)	41.3 (31.4)
PE / no complications	16.1 (10.2)	36 (27.3)
PE / major bleed due to treatment	22.1 (13.9)	49.4 (37.5)

We assumed that DVT prophylaxis would begin on day 1 and continue for the duration of the hospital stay for all patients not experiencing any complications. We also assumed that any DVT or prophylaxis related bleed occurred on day 5 of the hospital stay, and that any treatment related bleed occurred on day 3 of active treatment. The length of stay (LOS) in the intensive care unit (ICU) and

on the general ward were derived from the Canadian Institute for Health Information (CIHI) Ontario Trauma Registry (OTR) for 2002, stratified by whether or not they experienced a DVT (total sample n=3,696). Because the sample size and event rates precluded the sub-stratification by the occurrence of a major bleed or PE, the LOS for patients experiencing these

events was derived by adjusting the LOS for patients with and without a DVT or PE determined from the OTR data using ratios of the LOS for each subgroup (a major bleed without a DVT, a DVT or PE treatment-related bleed; or a PE) reported previously by O'Brien and Caro.²¹

The cost of B-mode U/S, 2 view-portable chest x-ray, spiral CT, and a bed day in both the ICU and on a medical ward were determined using the fully allocated cost model from the London Health Sciences Centre in London, ON, Canada. The analysis was performed from the perspective of the health-care payer; therefore, only direct costs incurred during the hospital stay were included.

Probabilistic Cost-Effectiveness Analysis

We performed a probabilistic cost-effectiveness analysis, which entails specifying a distribution for each model parameter to represent the uncertainty around the point estimate, and then selecting values at random from those distributions using Monte Carlo simulation.^{22,23} Distributions were included for all model parameters except costs. The uncertainty around model probabilities was represented using the beta distribution which is bounded by zero and one, and can be specified by α , the number of individuals experiencing an event, and β , the number of individuals not experiencing an event.²⁴ Where specific α and β parameters were not available, different beta distributions were specified assuming the probability was derived from $n=50, 100, 500, \text{ and } 1,000$ subjects. Because LOS is generally skewed to the left, a log normal distribution was applied.

Life Years Gained

Using the mean age (39 years) and gender distribution (28% female) of patients enrolled in the clinical trial,²⁵ we assumed that either a patient would die from complications on the last day of their hospital stay or would recover completely, be discharged from hospital, and live to the expected age of death based on 1997 Canadian life tables.²⁶ Life expectancy from 39 years of age was estimated for both women (43.32 years) and men (38.35 years) and then discounted at a rate of 5% per annum.

Sensitivity Analysis

In addition to evaluating parameter uncertainty using probabilistic analysis, we used one- and two-way deterministic sensitivity analysis to examine the impact of variability in model parameters that can be known with certainty, but may vary, such as costs (e.g. drug, treatment, diagnostic testing, nursing time, daily hospital stay) and discount rate. Two-way sensitivity analysis was used for length of stay costs by varying both the costs of ICU and medical ward concurrently. The variability in these model parameters was either varied over the range of estimates for the parameters obtained from different published sources, or by 25% above and below the point estimate.

RESULTS

Efficacy and Safety

Only one study was identified comparing UH to enoxaparin for the prophylaxis of DVT in trauma patients with an ISS of ≥ 9 .²⁵ In this study, 20/136 (14.7%) in the UH group and 8/129 (6.2%) ($p=0.012$) in the enoxaparin group experienced a proximal DVT, while 1/129 (0.7%) and 5/136 (3.7%) experienced a major bleed ($p=0.12$), respectively. The authors of this study concluded that enoxaparin was superior to UH in efficacy and that there was no difference in the rates of major bleeds.

We estimated that among patients who receive UH for DVT prophylaxis, the mean rates of DVT and PE would be 147.0 and 3.0 per 1,000 patients treated, respectively. The corresponding rates in patients receiving enoxaparin were 61.2 DVTs and 1.2 PEs per 1,000 patients treated. However, despite the non-statistically significant difference in the proportion of patients experiencing a major bleed in the clinical trial ($p=0.12$), the rates of major bleeds in patients receiving UH and enoxaparin were 8.4 and 38.8 per 1,000, respectively. Because the conditional probability of death, given the occurrence of a major bleed due to prophylaxis ($p=0.25$), is greater than the conditional probability of death from either a PE or treatment related bleed given that a DVT occurred ($p<0.001$), the overall mortality rate was higher in the enoxaparin group (10.1 versus 3.1 per 1,000). This resulted in 16.92

LYG per patient treated with enoxaparin versus 17.05 LYG per patient treated with UH.

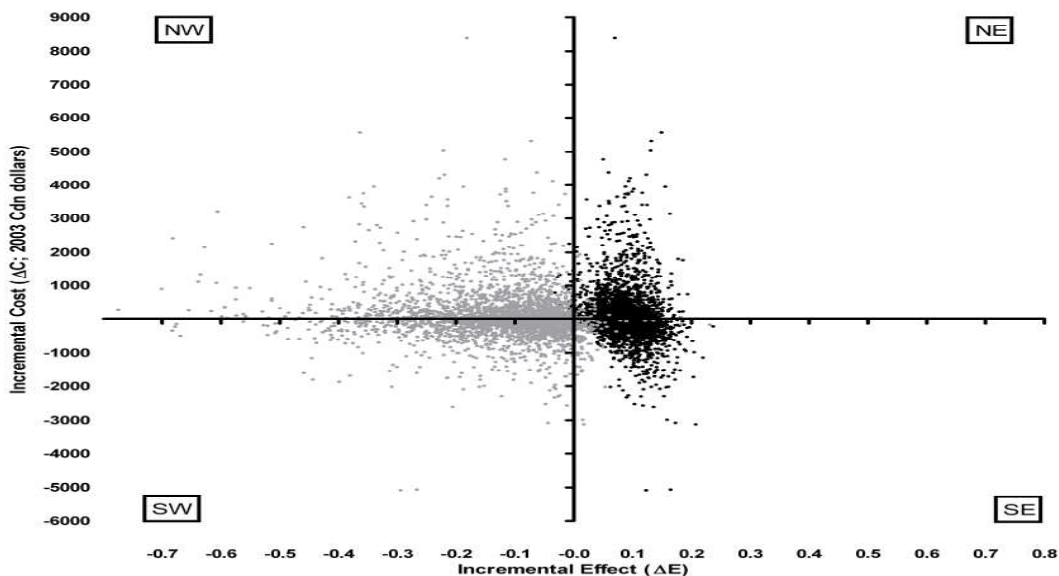
Cost-Effectiveness Analysis

The mean total cost of the hospital stay for enoxaparin-treated patients was \$12,686 per patient versus \$12,596 for UH patients. Although enoxaparin resulted in a lower mean cost of diagnosis and treatment of DVT and PE (\$58.30 versus \$72.40 per patient), this difference was more than offset by the additional cost of prophylaxis (\$229 versus \$123) and a longer mean ICU stay due to major bleeds. Thus, the enoxaparin regimen resulted in a ΔC of \$90. The incremental effectiveness (ΔE) differed depending upon the outcome metric applied, with enoxaparin being more effective in terms of DVTs averted (0.085, or 85 per 1,000 patients) resulting in an incremental cost-effectiveness ratio (ICER) of \$1,059 per DVT averted. In terms of LYG, because enoxaparin was more costly and less effective, an ICER cannot be calculated. However, this suggests that UH is the dominant strategy (i.e. the point estimate of $\Delta C/\Delta E$ falls in

the NW quadrant of the incremental cost-effectiveness plane).

The results of 3,000 iterations of the model are illustrated in Figure 3 as the joint density of ΔC and ΔE for both DVTs averted and LYG. Because the ΔC is independent of the outcome, approximately 50% of the ICERs from each simulation fall above the horizontal axis (i.e. in the north quadrants). Applying DVTs averted as the outcome metric resulted in 98% of the iterations falling to the right of the vertical axis (i.e. in the east quadrants), reflecting the probability that enoxaparin is more effective relative to UH for the prevention of DVTs. Furthermore, the probability that enoxaparin is both less costly and more effective is 0.51, based on the proportion of the joint density in the SE quadrant. However, using LYG as the outcome, only 5% of the joint distribution falls in the east quadrants, reflecting the low probability that enoxaparin is more effective than UH. Furthermore, 46.9% of the model iterations fall in the NW quadrant, illustrating the probability that UH is actually the dominant strategy (i.e. less costly and more effective than enoxaparin).

FIG. 3 Incremental Cost-Effectiveness Plane Displaying the Results of 3000 Iterations of the Model Comparing Enoxaparin to Unfractionated Heparin

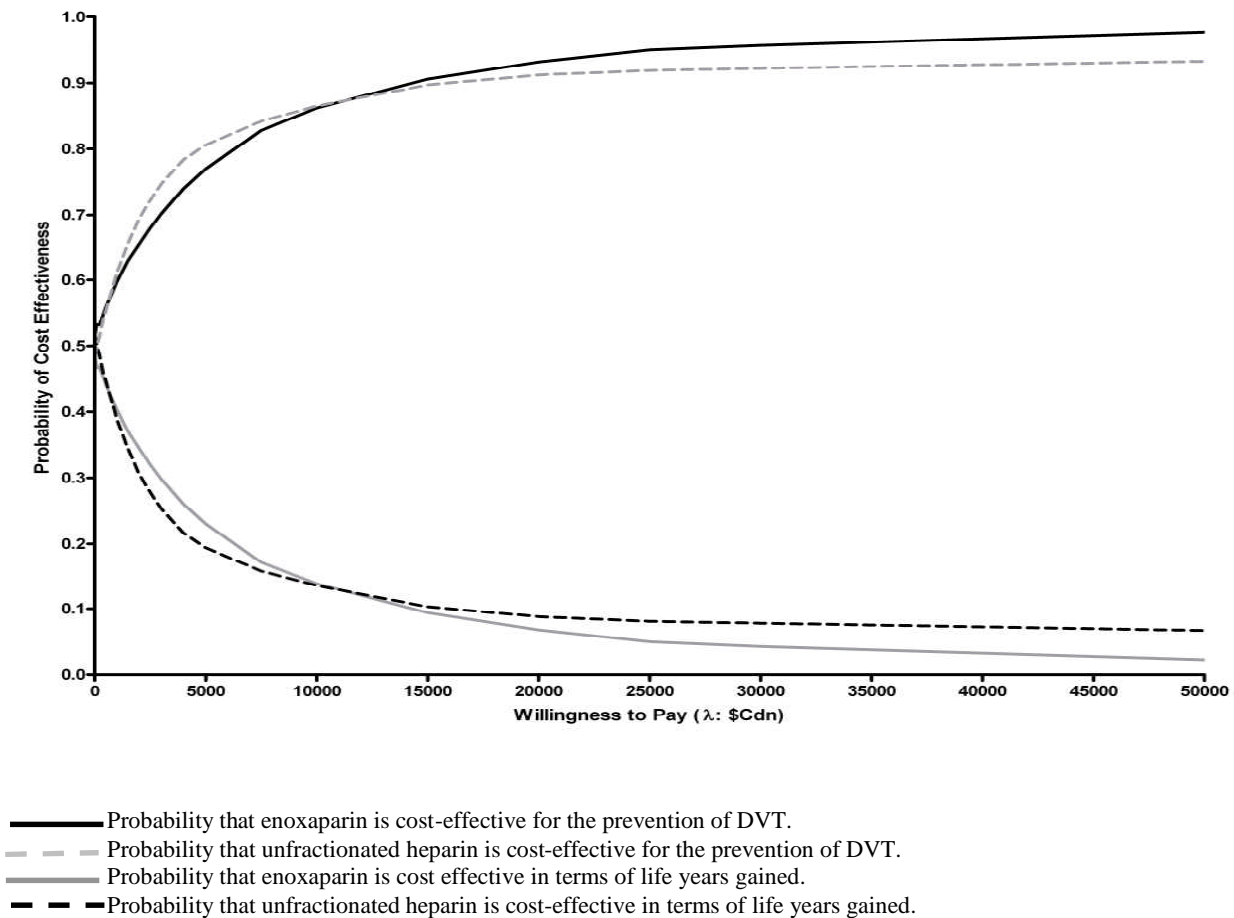


Each point represents the incremental cost-effectiveness ratio (ICER) of enoxaparin to unfractionated heparin derived from one iteration of the model. ● represents the incremental cost per DVT averted; ● represents the incremental cost per LYG derived from each individual iteration of the model

The decision whether or not to adopt a new therapy is dependent upon the willingness to pay (WTP; λ) for more benefit. Figure 4 illustrates the probability that either agent is cost effective, as function of λ .²⁷ In the base case where λ is assumed to be zero, there is approximately an equal probability that either agent is cost-effective, independent of the outcome. However,

as λ increases, the probability that enoxaparin is cost effective for preventing DVTs increases such that when $\lambda = \$20,000$ per DVT averted, there is 93% chance that enoxaparin will be cost-effective. However, the results are reversed in terms of LYG where there is 91% chance that UH is the most cost effective strategy when $\lambda = \$20,000$ per LYG.

FIG. 4 Cost-Effectiveness Acceptability Curves



Sensitivity Analysis

Deterministic sensitivity analyses revealed that our model was robust to the parameter estimates incorporated into the model. Varying the discount rate from 3% to 7% had the greatest impact on the LYG, which ranged from -0.10 to -0.17, respectively, but remained negative. Discount rate did not affect the incremental costs as all costs were incurred during the hospital stay.

Although all sensitivity analyses had a minor effect on the ICER, in all instances UH remained the dominant strategy. Varying the α and β parameters, assuming the probabilities were derived from different sample sizes for those variables for which these values were not available, did not affect the results.

DISCUSSION

For this cost-effectiveness analysis, we used all available data to address the question of the cost-effectiveness of enoxaparin versus UH for the prophylaxis of DVT following major trauma. Given the superior efficacy of enoxaparin relative to UH in preventing DVTs, using DVTs averted as the effectiveness metric resulted in an ICER of C\$1,059 per DVT averted. Based on this, one could conclude that enoxaparin is a cost-effective strategy. However, the development of a DVT is an intermediate endpoint, with mortality being the final endpoint, which occurs as a result of either a PE subsequent to a DVT, or following a treatment or prophylaxis-related major bleed. Although, as expected, our model predicts fewer DVTs in the enoxaparin arm, there were also more deaths in this arm as a result of the higher rate of major bleeds, which subsequently resulted in higher mortality and 0.13 fewer LYG per 1,000 patients treated. Sensitivity analyses revealed that our model was robust to the variation of all model parameters, and thus, independent of the modeling assumptions invoked. UH may be the dominant strategy (less costly, more effective) relative to enoxaparin for this indication. In general, this analysis highlights the need to balance model parsimony with comprehensiveness, and the need to ensure that most appropriate metric of effectiveness is evaluated. This also highlights the potential impact of economic analyses that are based on short-term, randomized controlled trial data, and surrogate efficacy endpoints that are underpowered to detect statistically significant differences in adverse event rates rather than long term endpoints.

The hallmark randomized clinical trial that compared enoxaparin to UH concluded that enoxaparin was more beneficial without any difference in major bleeding rates.²⁵ There have also been two previously published CEAs evaluating these two prophylactic modalities specifically in this clinical situation, both of which also used the same RCT as the basis for modeling outcomes.²⁵ Shorr and Ramage only evaluated the ΔC per DVT averted and concluded that enoxaparin was the dominant strategy, producing an ΔC of -\$28,755 per 1,000 patients treated and a ΔE of -73.5 DVTs.²⁸ However, their model was based entirely on the clinical trial results and

therefore included all venographically detected DVTs rather than incorporating potential diagnostic inaccuracy into the model, which is more representative of clinical practice. Additionally, they limited their effectiveness analysis to DVTs averted, thereby neglecting the cost and outcome consequences of PE, major bleeds, and death.

Devlin et al. developed a decision analytic model that incorporated diagnostic accuracy and the incidence of PE and PE-related mortality.²⁹ Using a combined endpoint of DVTs and PEs averted, their model produced an ICER of US\$1,684 per DVT or PE averted, and US\$2,300 per life year saved. Although their results were consistent with ours in terms of DVTs averted, they differed from ours in term of LYG, which may be due to their omission of the risk of major bleeding and mortality associated with prophylaxis and treatment-related major bleeds from their model.

Cost-effectiveness analysis based on economic modeling have been criticized;³⁰ but, modeling is often an unavoidable necessity when outcomes must be extrapolated beyond the results of a clinical trial, or intermediate clinical endpoints must be linked to final outcomes.³¹ Although the results of this analysis may be criticized based on their basis on modeling, the recommendations of the 7th American College of Chest Physicians conference on antithrombotic and thrombolytic therapy state that the results of the two previous models “support the superiority of LMWH over UH prophylaxis in high-risk trauma patients”, despite their limitations.³² We believe our model follows the principles of good economic modeling practice, and is the most comprehensive to date.³³

This analytic framework also demonstrates the benefits of employing a Bayesian versus a frequentist interpretation of clinical trial data. Whereas, the previous two models appear to have relied upon the frequentist interpretation of the RCT (with an arbitrary α error threshold of 0.05) and therefore excluded the clinical implications of a major bleeding event based on the conclusion of no difference between groups, we incorporated all data available from the clinical trial, and the associated second order uncertainty. Thus, incorporating all available data into the model not only provides additional evidence of the cost-

effectiveness of enoxaparin, it also brings into question the frequentist interpretation of the RCT of no difference in major bleeding rates despite 5/136 and 1/129 major bleeds in the enoxaparin and UH groups, respectively. Furthermore, it illustrates the potential consequences of clinical conclusions based on intermediate, rather than, final endpoints.

In the absence of a large, long-term RCT that incorporates all final endpoints and measurement and costing of health care resource utilization, this modeling study, involving a synthesis of all available evidence, is the most comprehensive and methodologically sound CEA of enoxaparin versus UH following trauma published to date. Although all previously published clinical and economic analyses concluded that enoxaparin is superior to UH, this analysis from a Bayesian perspective highlights the importance of considering outcomes that may not have occurred in the randomized control trial, due to either the length or size of the study, and brings the conclusions of the previous analyses into question.

Acknowledgements

Dr. Lynd was a post-doctoral fellow at the Program for Assessment of Technology in Health, McMaster University in Hamilton, ON, Canada and the recipient of a Canadian Institutes for Health Research post-doctoral fellowship while undertaking the analysis for the study. He is also currently a Career Investigator of the Michael Smith Foundation for Health Research. Dr. Crowther is a Career Investigator of the Heart and Stroke Foundation of Ontario. No other funds for the study were received.

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