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Economic Evaluation of Unfractionated Heparin Versus Low-Molecular-Weight Heparin to Prevent Venous Thromboembolism in General Medical and Non-Orthopedic Surgical Patients

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Braden Manns participated in the conception and design of the economic evaluation, and participated in the analysis and interpretation of results and report revisions.

Marcello Tonelli participated in the conception and design of the economic evaluation, and participated in the analysis and interpretation of results and report revisions.

All authors approved the final draft report.

Contributors

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Conflicts of Interest

Dr. Marc Carrier received honoraria for speaking engagements from Sanofi-Aventis, Pfizer, Boehringer Ingelheim, LEO Pharma, and Bayer. He received research funding from LEO Pharma and Bristol-Myers Squibb and was a consultant for Scientific Advisory Board meetings for Sanofi-Aventis and LEO Pharma.

Dr. William Geerts received funding for lectures from Bayer Healthcare (including a venous thromboembolism [VTE] toolkit), LEO Pharma, Pfizer, and Sanofi, and received funding for developing a module for VTE prevention for GlaxoSmithKline. He consulted for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, LEO Pharma, Pfizer, and Sanofi.

Dr. Agnes Lee received honoraria for educational lectures from Bayer, Boehringer Ingelheim, Pfizer, and Sanofi- Aventis. She received research funding and/or consulted for Bayer, Bristol-Myers Squibb, Daiichi Sankyo, LEO Pharma and Pfizer. She provided reviews and advice for the Guidelines and Protocols Advisory Committee for the Doctors of BC and the British Columbia Ministry of Health.

No other conflicts of interest were declared.

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Key Finding: Economic Evaluation

- The price of low-molecular-weight heparin (LMWH) has decreased since it was marketed in the mid-1990s in Canada, while unfractionated heparin (UFH) has recently become more costly because of changes in the manufacturing process to ensure safety. At current list prices, the difference in drug acquisition cost between UFH and LMWH is small (estimated difference of $1.20 per day), with UFH being slightly less costly.
- While the differences in both drug acquisition costs and clinical outcomes between LMWH and UFH are small, there are approximately three million hospitalization episodes in Canada per year. As such, these small differences in cost could have a large economic impact.
- In light of changes in the cost of drugs used to prevent venous thromboembolism (VTE) in hospitalized patients, an economic evaluation was conducted to determine the incremental cost-effectiveness of LMWH compared with UFH for the prevention of VTE in medical and non-orthopedic surgery patients who are hospitalized.
- In the reference case, the differential risk of heparin-induced thrombocytopenia (HIT) with or without thrombosis (HITT) due to treatment with LMWH compared with UFH was not included, as these outcomes could not be assessed in the studies included in the clinical review. However, given the importance of this outcome, the inclusion of HITT was considered in scenario analyses.
    - In surgical patients, when the impact of HITT is not considered, LMWH is associated with higher drug acquisition costs and higher bleeding-related costs (see clinical report),[1] which results in UFH being the dominant strategy (less costly and more effective than LMWH).
    - In medical patients, when HITT is not considered, LMWH is associated with a reduced risk of VTE, resulting in lower costs attributable to this complication and greater clinical benefits compared with UFH (i.e., LMWH is dominant). The cost savings arising from averting VTEs outweigh the slight differences in drug costs. While these results are robust in most sensitivity analyses, the LMWH strategy is more costly (and remains more effective) if the price paid for LMWH (or the relative price compared with UFH) is greater than estimated for the reference-case analysis.
- When considering a scenario analysis that includes HITT, and using the best available data on the baseline risk of HITT, the probability of HITT with LMWH and UFH (where the risk of HITT is lower for LMWH than UFH) and the costs of HITT indicate that HITT is a primary driver of the economic analysis.
    - In most analyses that considered both surgical and medical patients, LMWH was dominant over UFH (less costly and more effective than UFH), as it reduced the occurrence of the serious and costly complication of HITT. This conclusion was largely unchanged in sensitivity analysis that considered alternate baseline risks of HITT, relative risk (RR), and costs.
    - In surgical patients, the incremental drug costs and bleeding complications of LMWH are outweighed by cost savings

attributable to the reduced risk of developing HITT. Further, LMWH results in greater clinical benefit due to averting death due to HITT. These conclusions hold in most sensitivity analyses, except when the very lowest estimate of the baseline risk of HITT is used, at which point LMWH becomes more costly and more effective than UFH.

        - When a subgroup of surgical patients with cancer is evaluated (without including HITT), there is no difference in costs attributable to bleeding, as no difference in the risk of bleeding was found in the clinical review. UFH remains preferred, as the daily drug cost is slightly lower. When HITT is incorporated, LMWH is dominant.

    - In medical patients, LMWH remains dominant (more effective and less costly) compared with UFH. This result is unaltered in sensitivity analyses, including plausible ranges of drug acquisition costs.

        - In a subgroup of medical patients without stroke, no difference in the occurrence of VTE was found. As such, UFH is preferred because of the slightly lower drug cost when the occurrence of HITT is not incorporated in the analysis. When HITT is included, LMWH is less costly and more effective than UFH because of the associated reduced risk in developing HITT, a finding that remains unchanged in sensitivity analysis.

- Available data suggest that (assuming LMWH reduces the risk of HITT compared with UFH) LMWH is the preferred strategy to prevent VTE in hospitalized medical or surgical patients compared with UFH, even if it increases the risk of bleeding in surgical patients.

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Abbreviations

CI	confidence interval
CTEPH	chronic thromboembolic pulmonary hypertension
DVT	deep vein thrombosis
HIT	heparin-induced thrombocytopenia
HITT	heparin-induced thrombocytopenia and thrombosis
LMWH	low-molecular-weight heparin
OR	odds ratio
PE	pulmonary embolism
PTS	post-thrombotic syndrome
QALY	quality-adjusted life-year
RR	relative risk
UFH	unfractionated heparin
VTE	venous thromboembolism

Background

Deep vein thrombosis (DVT) and pulmonary embolism (PE) constitute venous thromboembolism (VTE), which is common in hospitalized patients and is a major source of morbidity and mortality in both medical and non-orthopedic surgery patients. VTE is one of the most common preventable causes of in-patient mortality; among more than seven million patients discharged from 944 North American acute care hospitals, post-operative VTE was the second most common medical complication, the second most common cause of excess length of stay, and the third most common cause of excess mortality and costs. As such, strategies to reduce the occurrence of VTEs are critical in at-risk patients, and prophylactic administration of heparin has emerged as a standard of care.

The two most common options are unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). While some studies have concluded that the efficacy and safety of UFH and LMWH are similar, others have suggested there may be differences in their clinical effectiveness and safety, including risks of bleeding and heparin-induced thrombocytopenia (HIT). From a health care resource-utilization perspective, in the past, the drug acquisition costs of UFH have typically been substantially lower than LMWH. However, due to price reductions in LMWH and the recent increases in the cost of UFH resulting from higher manufacturing costs to ensure safety,[2] the difference in drug costs is decreasing. Given the widespread use of heparin-based VTE prophylaxis, even small differences in outcomes and costs may have significant clinical and economic implications.

Given these considerations, the selection of a VTE prevention pharmacologic option is an important decision, both from a hospital formulary and a clinical perspective. In order to inform decision-making within provincial and territorial regional health authorities (RHAs) and hospitals, a health technology assessment (HTA) of anticoagulants for the prevention of VTE in the hospital setting was undertaken. This HTA project was a collaboration between the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research and CADTH. A research group affiliated with DSEN (the University of Ottawa Heart Institute Cardiovascular Research Methods Centre [UOHI-CRMC]) conducted a systematic review comparing the clinical efficacy and safety of UFH and LMWH in preventing VTE in hospitalized medical and surgical (non-orthopedic/general abdominal surgery) patients.[1] CADTH conducted an economic evaluation to determine the cost-effectiveness of LMWH versus UFH for the prevention of VTE in the same populations. This report provides results from the economic evaluation; results from the clinical review are available in a separate report.[1]

Primary Economic Evaluation

The objective of the economic evaluation is to determine the incremental cost-effectiveness of LMWH compared with UFH for the prevention of VTE in hospitalized general surgical or medical patients.

Methods

Type of Economic Evaluation

As VTE and the potential harms of prophylaxis may impact both quality of life and mortality, a cost-utility analysis was conducted where health outcomes were quantified using quality-adjusted life-years (QALYs). Incremental costs and QALYs of alternate treatments were determined.

Target Population

The target population for VTE prevention was based on the weighted average of characteristics of adult patients who were enrolled in the randomized clinical trials included in the clinical systematic review for in-hospital prevention of VTE done by UOHI-CRMC.[1]

For general surgical patients (abdominal or pelvic cancer, colorectal surgery), simulated patients were an average age of 59 years, and 53% were male. The clinical review results stratified the analysis into patients with cancer and those without cancer; these two subgroups of surgical patients were considered in the sensitivity analyses.

For medical patients, simulated patients were an average age of 73 years, and 51% were male. In the clinical review, results were stratified by stroke versus non-stroke patients; these two subgroups of medical patients were also considered in the sensitivity analyses.

It was assumed that patients enrolled in clinical trials had characteristics similar to Canadian in-patients developing VTE.

Treatment Comparators

The following treatments were considered in the model (Table 1). Of note, the drugs, doses, and treatment durations included in the scope of this economic evaluation reflect the policy questions posed by CADTH's jurisdictional clients; input from clinical experts was also considered to ensure the clinical relevance of the report in Canada. UFH administered subcutaneously twice daily for an average duration of 10 days was used as the "standard of care" strategy, recognizing that there is variability in the use of UFH in Canada.

The comparator strategy was LMWH, specifically, enoxaparin 40 mg subcutaneously once daily (reference case) for an average duration of 10 days. Other LMWH products were considered in alternate analyses (although, given the lack of evidence of differing efficacy among LMWHs, only variation in cost was considered).

Table 1: Treatment Comparators

Treatment	Strategy
UFH	Unfractionated heparin 5,000 IU twice daily Unfractionated heparin 5,000 IU three times daily
LMWH	Enoxaparin 40 mg Dalteparin 5,000 IU daily Tinzaparin 3,500 or 4,500 IU daily Nadroparin 2,850 IU daily

IU = international units; LMWH = low-molecular-weight heparin.

Note: Alternate LMWH included enoxaparin 20 mg daily or 30 mg twice daily; dalteparin 2,500 IU or 5,000 IU daily; tinzaparin 3,500 IU daily; and nadroparin 2,850 IU daily.

Audience and Perspective

The target audiences considered were provincial and territorial RHAs as well as hospitals.

The analysis was conducted from a Canadian ministry of health perspective, consistent with CADTH guidelines.[3]

Patient productivity was not incorporated into the analysis; patient preferences are included in quality-of-life considerations. Incremental differences in productivity may occur; however, given that the primary impact of prophylaxis is on events that have their major impact in the short term (VTE, bleeding, HIT) in a hospitalized population, they are likely to be minor.

Time Horizon

The majority of the clinical and economic consequences of preventing VTE in hospitalized patients occur within the first three months, although there may be long-term consequences related to VTE and its treatment. In the reference case, a time horizon of three months following index hospitalization was considered. Longer time horizons of a lifetime time horizon (39 years for surgical patients and 21 years for medical patients) were assessed in the sensitivity analysis.

Discount Rate

Costs and benefits were discounted at 5%, and rates of 0% and 3% were tested in the sensitivity analysis.[3]

Modelling

A combination of a decision tree and a Markov model was created to examine the two cohorts: hospitalized medical patients and hospitalized non-orthopedic surgical patients who are at risk for VTE and require VTE prevention therapy. The decision tree captured events during index hospitalization, and the Markov model considered health states after discharge and long-term consequences.

A decision tree was used to track events during hospitalization where the patients received either LMWH or UFH prophylaxis therapy.

Patients may experience one or more of the following events during hospitalization:

- VTE, either DVT or PE (± DVT)
- major or minor bleeding from prophylaxis
- HIT or HITT
- death.

Patients then entered the long-term Markov model that considered post-discharge consequences. For each one-month cycle, patients transitioned through various health states related to previous health states in the decision tree. Health states included:

- "healthy" state — patients who did not experience a VTE or a complication that later resolved (HITT, bleed, or VTE)
- continued treatment required — patient needing treatment for hospital-acquired DVT, or PE with systemic anticoagulation. Patients may have experienced attendant complications of systemic anticoagulation, including major or minor bleeding. VTE and treatment were based on a previous model developed for an assessment of direct oral anticoagulants for treating VTEs[4]
- death.

Other events, including myocardial infarction, ischemic stroke, and non-central nervous system systemic embolism, were not included in the model, as these are uncommon events and available data do not suggest that choice of strategy for VTE prevention influenced their risk.[1]

Clinical Events

Hospital-Acquired Venous Thromboembolism (Deep Vein Thrombosis or Pulmonary Embolism)

It was assumed that for patients who develop VTE, confirmatory diagnostic tests would be conducted and patients would be started on treatment doses of LMWH followed by warfarin for a total duration of three months (use of direct oral anticoagulants, e.g., dabigatran or rivaroxaban, was tested in sensitivity analyses). Patients with VTE have an increased risk of death (due to PE), and are also at risk for major or minor bleeding. Treatment-related major bleeding is further sub-classified into either major extracranial or intracranial hemorrhage. The cost and consequences of major extracranial bleeding were assumed to be captured by the clinical state of a major gastrointestinal bleed. The approach to modelling VTE and its treatment was adapted from a previous model.[4]

Prophylaxis-Associated Major or Minor Bleeding

The consequences of bleeding due to treatment with prophylaxis were obtained from definitions from the trials (where stated) included in the UOHI-CRMC clinical review and from expert opinion. Minor bleeding was assumed to result in no significant clinical or resource-use consequences. Major bleeding was assumed to result in the

transfusion of two units of blood and an additional three days of hospitalization for managing and monitoring of bleeding.

Heparin-Induced Thrombocytopenia With or Without Thrombosis

The consequences of HIT/HITT were obtained from literature reports[5,6] and expert opinion. Simulated patients were managed by stopping LMWH or UFH. For patients with HIT only, administration of a HIT-safe parenteral anticoagulant (such as argatroban, bivalirudin, lepirudin, danaparoid, or fondaparinux) was initiated, followed by the administration of oral warfarin for up to one month; patients incurred one additional hospital day.

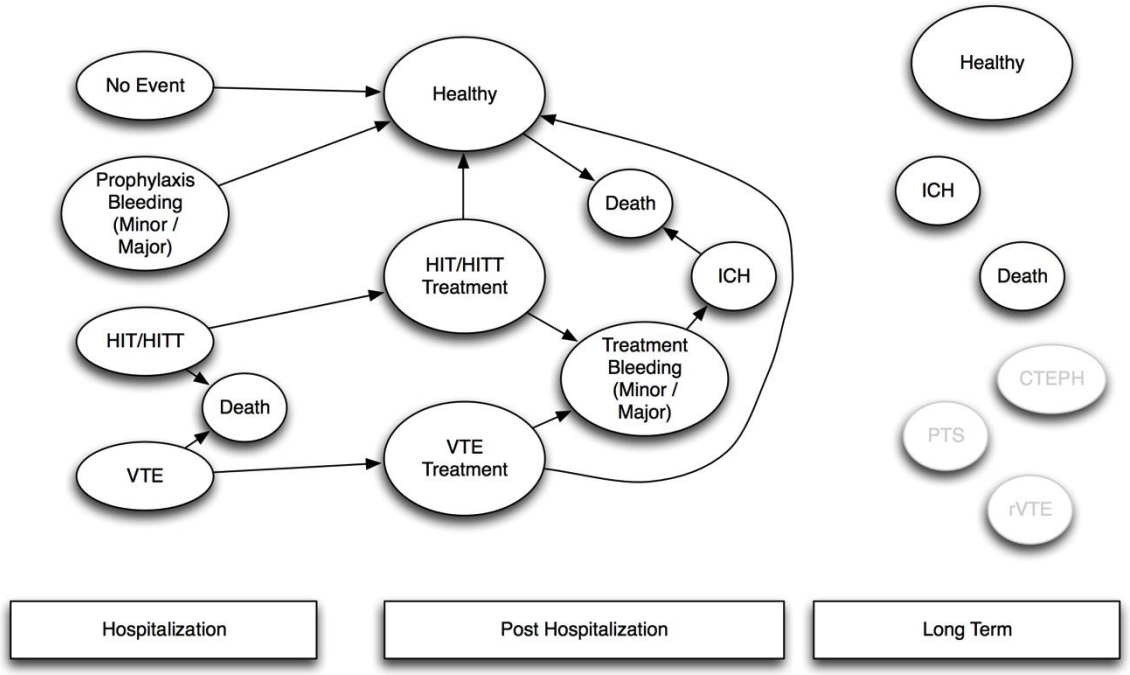
Patients with HITT were assumed to have a longer duration of treatment with a HIT-safe anticoagulant followed by warfarin (three months), and to have stayed in hospital an additional seven days. Patients with HITT were assumed to have an increased risk of death during hospitalization.[7,8] It was assumed there would be no longer-term consequences for survivors of HITT, which likely underestimated the impact of this complication, as a small proportion of patients may have chronic health and resource-use implications as a consequence of venous or arterial thrombosis.

Post-Thrombotic Syndrome and Chronic Thromboembolic Pulmonary Hypertension

A subset of patients may have chronic consequences of a VTE event, which are associated with longer-term health care costs and health impact. In the reference case, these consequences were not incorporated, but were tested in a sensitivity analysis using the same approach and parameters as used in a prior economic analysis.[4]

The conceptual design of the model is detailed in Figure 1.

Figure 1: Overview of Economic Model



CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep venous thrombosis; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; ICH = intracranial hemorrhage; PE = pulmonary embolism; PTS = post-thrombotic syndrome; rVTE = recurrent venous thromboembolism; VTE = venous thromboembolism.

The following model assumptions were made:

- Prophylaxis-associated major bleeding resulted in a longer length of stay and need for transfusion, but there was no impact on minor bleeding. As the complication of bleeding is self-limited and occurs in already-hospitalized patients, it was assumed the impact on quality of life was negligible.
- While HITT can be associated with significant long-term clinical consequences, these events are uncommon, and the true magnitude of these consequences is not clear. While an increased risk of mortality was incorporated for the acute event, long-term post-discharge events were not included. Further, as HITT occurs in hospitalized patients, no additional disutility was applied.
- The clinical and resource-use complications of VTE and its treatment are similar to VTEs that occur in other contexts. Information on these complications was obtained from a previous CADTH publication on VTE treatment,[4] and it was assumed that such patients would be treated with full-dose LMWH (administered during admission), followed by warfarin.

Model Inputs

Mortality

After discharge, patients may transition to the death state from any health state. All-cause mortality was informed by Canadian life tables to estimate survival for patients after surgery or medical admissions.[9] This may underestimate true mortality, as it is likely that, on average, medical or surgical patients have a risk of death that is greater than the general population. Mortality data on this group of patients are not readily available but, given that most of the impact of VTE and prevention strategies occurs in the short term, this likely did not bias results. Patients experiencing an event related to VTE or systemic anticoagulation have a risk of mortality, as determined from a previous review.[4]

Baseline Probabilities and Relative Efficacy and Safety (Table 2 to Table 6)

Where possible, baseline probabilities for the medical and surgical cohorts were obtained from the clinical systematic review.[1] The baseline probability of a VTE event was not obtained from the clinical studies, as some trials used specific outcome measures for detection that may not occur in routine clinical practice. As such, the probability of VTE was obtained from the weighted average of observational studies identified from a focused literature search for both medical and non-orthopedic surgical patients.[10-21] The probability of HITT was obtained from literature sources and expert opinion, as it was not an outcome in studies included in the clinical review.[7,8,10-33] The probability of clinical events associated with VTE and its treatment was obtained from a previous systematic review and economic evaluation.[4]

Table 2: Short-Term Parameters (Three Months) — Non-Orthopedic Surgical Patients Receiving Unfractionated Heparin

Variable Description	Base Estimate	Lower 95% CI (Min)	Upper 95% CI (Max)	Probability Distribution	Source	Comment
Months 0 to 3 With UFH (Probability Over 3 Months) Prophylaxis-Related						
Probability of bleed from prophylaxis	0.065	—	—	Beta (42/643)	Clinical report	
Proportion of bleeding from prophylaxis that is major	0.25	0.013	0.099	Beta (28/112)	Clinical report; observational studies (Kwon et al. and Agnelli et al.)[13,20]	
Probability of VTE	0.0159	0.0012	0.0247	Beta	Weighted average from observational studies[10-20]	Clinically important VTE from observa-tional data

Variable Description	Base Estimate	Lower 95% CI (Min)	Upper 95% CI (Max)	Probability Distribution	Source	Comment
Months 0 to 3 With UFH (Probability Over 3 Months) Prophylaxis-Related						
Proportion of DVT given a VTE	0.284	—	—	Beta (25/88)	Prophylaxis NMA	
Probability of HIT	0.02	0.02	0.0291	Beta	Expert opinion; Junqueira et al.[21]	

CI = confidence interval; DVT = deep vein thrombosis; HIT = heparin-induced thrombocytopenia; NMA = network meta-analysis; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 3: Short-Term Parameters (Three Months) — Medical Patients Receiving Unfractionated Heparin

Variable Description	Base Estimate	Lower 95% CI (Min)	Upper 95% CI (Max)	Probability Distribution	Source	Comment
Months 0 to 3 With UFH (Probability Over 3 Months) Prophylaxis-Related						
Probability of bleed from prophylaxis	0.0628	—	—	Beta (85/1,354)	Clinical review	
Proportion of bleeding from prophylaxis that is major	0.107	0.0026	0.016	Beta (18/169)	Clinical review; observational studies (Flanders et al. and Barbar et al.)[22,29]	
Probability of VTE	0.007	0.0015	0.012	Beta	Weighted average from observational studies[22-29,33]	Clinically important VTE from observational data
Proportion of DVT given a VTE	0.97	—	—	Beta (228/236)	Clinical review	
Probability of HIT	0.01	0.0002	0.027	Beta	Leykum et al.[7]; Rothberg et al.[26]; Deitelzweig et al.[30]	

CI = confidence interval; DVT = deep vein thrombosis; HIT = heparin-induced thrombocytopenia; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 4: Short-Term Parameters (Three Months) — Surgical and Medical Patients

Variable Description	Base Estimate	Lower 95% CI (Min)	Upper 95% CI (Max)	Probability Distribution	Source	Comment
HITT-Related						
Probability of HIT (for UFH)	0.01 (medical) 0.02 (surgical)	0.00165	0.026	Beta	Expert opinion Junqueira et al.[21]; McGowan et al.[31]; Martel[32]; Leykum et al.[7]; Rothberg et al.[26]; Deitelzweig et al.[30]	
Proportion of HIT with thrombosis (HITT)	0.35	0.04 (LMWH)	0.43	—	Expert opinion; Baroletti et al.[8]; McGowan et al.[31]	
Probability of death for HIT	0	—	—	—	Expert opinion	
Probability of death for HITT	0.08	0.08	0.207	—	Leykum et al.[7]; Baroletti et al.[8]	
VTE Treatment-Related						
Probability of bleed from VTE treatment[a]	0.0486	—	—	Normal	VTE treatment model	
Proportion of major bleed (EC or IC bleed) given bleeding	0.139	—	—	Normal	VTE treatment model	
Proportion of IC bleed given major bleeding from VTE treatment	0.165	—	—	Normal	VTE treatment model	

CI = confidence interval; EC = extracranial; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; IC = intracranial; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

a For patients receiving full-dose systemic anticoagulation for treatment of VTE or HIT/HITT.

Table 5: Probabilities in the Long Term

Variable Description	Base Estimate	Lower 95% CI	Upper 95% CI	Probability Distribution	Reference	Comment
Months 3+ With UFH (Probability Over 1 Year)						
Probability of death with VTE	0.033	-	-	Normal	Schulman et al.[34]	

CI = confidence interval; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 6: Event-Related Probabilities

Variable Description	Base Estimate	Lower 95% CI	Upper 95% CI	Probability Distribution	Source	Comment
Probability that major bleed from VTE treatment is ICH	0.165			Beta (42/254)	VTE treatment model	
Probability of death for PE	0.0377	0.0110	0.0838	Beta (6/159)	VTE treatment model	
Probability of death for IC bleed	0.436	0.365	0.507	Beta (82/188)	Linkins et al.[35]	
Probability of death for EC bleed	0.039	0.027	0.054	Beta (27/689)	Linkins et al.[35]	
Long-Term Events (Tested in Scenario Analysis Only)						
Probability of PTS (in SA)	0.081	0.058	0.104	Beta (28/528)	Prandoni et al.[36]	For DVT
Probability of CTEPH (in SA)	0.0016	0.001	0.002	Beta (4/320)	Miniati et al.[37]	For PE
Probability of death for CTEPH (in SA)	0.0248	0.021	0.029	Normal	Condliffe et al.[38]	For PE

CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; IC = intracranial; ICH = intracranial hemorrhage; PE = pulmonary embolism; PTS = post-thrombotic syndrome; SA = sensitivity analysis; VTE = venous thromboembolism.

Relative Efficacy and Safety (Table 7 to Table 10)

The relative efficacy and safety of the two preventive treatments were obtained from the clinical systematic review and meta-analysis comparing UFH with LMWH.[1] Separate estimates were obtained from medical versus non-orthopedic surgical patients. For estimates where the 95% confidence intervals (CIs) overlapped unity, it was assumed there was no difference between the two treatment strategies. Subgroups of patients, including medical patients with or without stroke, and surgical patients with cancer, were also evaluated in sensitivity analyses.

It should be noted that some studies included in the clinical review frequently used outcome measures to ascertain VTE that may not reflect clinically apparent VTE. The clinical experts acting as advisors for this evaluation indicated that the odds ratio (OR), as ascertained in a clinical trial, is likely applicable to clinically relevant VTE. As such, the outcome of “all VTE” from the clinical review was used to assess relative efficacy.

A priori, the outcomes of “any VTE” and “all bleeding” were the primary efficacy and safety outcomes used in the economic model. This is a consideration for prevention-associated bleeding, as “any” bleeding was significant (OR, 1.72; 95% CI, 1.15 to 2.56); any minor bleeding was also significant (OR, 1.65; 95% CI, 1.05 to 2.60), however “major” bleeding was not (OR, 1.79; 95% CI, 0.82 to 3.92). A proportion of VTE would be either DVT or PE (± DVT) or major/minor bleeding respectively. That is, the OR for relative efficacy and safety apply to all VTE and all bleeding.

Note that no data on the occurrence of HITT by treatment strategy are available from the clinical systematic review, as this outcome was not reported in the included studies. In the reference case, it was assumed there was no difference between treatments for this outcome. The economic impact of differences in the risks of developing HIT/HITT between UFH and LMWH was explored in scenario analyses using data from systematic reviews identified through a supplemental literature search.

Table 7: Relative Efficacy and Safety (Odds Ratio) of LMWH Compared With UFH — Surgical Patients

Variable Description	Reference Case	Point Estimate (PSA)	Lower 95% CI	Upper 95% CI	Probability Distribution
OR for Any VTE					
LMWH	1.0	1.0	0.65	1.54	Lognormal
OR for Bleeding From Prophylaxis					
LMWH	1.72	1.72	1.15	2.56	Lognormal
OR/RR for HIT					
OR LMWH (combined) [32]	1.0	0.10	0.01	0.82	Lognormal
RR LMWH (surgical) [21]	1.0	0.24	0.07	0.82	Lognormal

CI = confidence interval; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; OR = odds ratio; PSA = probabilistic sensitivity analysis; RR = relative risk; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 8: Relative Efficacy and Safety (Odds Ratio) of LMWH Compared With UFH — Surgical Patients With Cancer

Variable Description	Reference Case	Point Estimate (PSA)	Lower 95% CI	Upper 95% CI	Probability Distribution
Odds Ratio for any VTE					
LMWH	1.0	0.88	0.65	1.18	Lognormal
Odds Ratio for Bleeding From Prophylaxis					
LMWH	1.0	1.36	0.89	2.07	Lognormal
Relative Risk for HIT					
LMWH[21]	1.0	0.24	0.07	0.82	Lognormal

CI = confidence interval; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; PSA = probabilistic sensitivity analysis; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 9: Relative Efficacy and Safety (Odds Ratio) of LMWH Compared With UFH – Medical Patients

Variable Description	Reference Case	Point Estimate (PSA)	Lower 95% CI	Upper 95% CI	Probability Distribution
Odds Ratio for any VTE					
LMWH	0.51	0.51	0.38	0.68	Lognormal
Odds Ratio for Bleeding From Prophylaxis					
LMWH	1.0	0.98	0.71	1.34	Lognormal
Odds Ratio for HIT					
LMWH[32]	1.0	0.10	0.01	0.82	Lognormal

CI = confidence interval; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; PSA = probabilistic sensitivity analysis; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 10: Relative Efficacy and Safety (Odds Ratio) of LMWH Compared With UFH — Medical Patients, Excluding Stroke

Variable Description	Reference Case	Point Estimate (PSA)	Lower 95% CrI	Upper 95% CrI	Probability Distribution
Odds Ratio for any VTE					
LMWH	1.0	0.14	0.02	1.16	Lognormal
Odds Ratio for Bleeding From Prophylaxis					
LMWH	1.0	1.01	0.46	2.20	Lognormal
Odds Ratio for HIT					
LMWH[32]	1.0	0.10	0.01	0.82	Lognormal

CrI = credible interval; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; PSA = probabilistic sensitivity analysis; UFH = unfractionated heparin; VTE = venous thromboembolism.

Utility Values (Table 11 to Table 12)

In the short-term, decision-tree component of the model, no changes in utility as a result of prophylaxis or its consequences were included (population norms were used). This is because patients receiving prophylaxis would have already been unwell and treated either medically or surgically for their underlying problem; the impact of an additional complication during this short period in hospital is not clear and is likely to be small. Furthermore, even large changes in quality of life occurring over a short time frame are likely to have minimal implications. This assumption also applies to HITT.

The exception is VTE and its treatment, where the disutility of DVT or PE, as well as the disutility of major or minor bleeding due to systemic anticoagulation for treatment, were included. This includes the rare but serious event of intracranial bleeding. Other consequences, including post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH), were included in the model, although in the reference case it was assumed that these states do not occur in hospital-associated VTE.

Table 11: Utility Values for Health States

Variable Description	Base Estimate	Lower Value	Upper Value	Distribution	Reference
Population norm	0.920	0.920	0.920	-	Maddigan et al. (2005)[39]
DVT[a] (1 month)	0.810	0.550	0.940	Normal	Hogg et al. (2013)[40]
PE[a] (1 month)	0.750	0.450	0.910	Normal	Hogg et al.(2013)
Severe PTS[a]	0.930	1.000	0.760	Normal	Lenert et al. (1997)[41]
EC bleed[a] (1 week)	0.650	0.150	0.860	Normal	Hogg et al. (2013)
IC bleed[a]	0.150	0.000	0.650	Normal	Hogg et al (2013)
Post-IC bleed	0.713	0.702	0.724	Normal	Rivero-Arias et al. (2010)[42]
CTEPH	0.560	0.528	0.592	Normal	
Bleeding from prophylaxis	0.920	0.920	0.920	-	Meads et al. (2008)[43]
HIT/HITT	0.920	0.920	0.920	-	Assumption[b]

CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; IC = intracranial; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; PE = pulmonary embolism; PTS = post-thrombotic syndrome.
[a] Applied to population norm utility value either indefinitely or for the anticipated duration of disutility in parentheses.
[b] Assumed no change to utility.

Table 12: Description of Studies Informing Utility Values

Variable Description	Reference	Population	Method	Country
Population norm	Maddigan et al. (2005)[39]	1996−1997 Canadian National Population Health Survey control group (n = 53,137)	ANCOVA to compare overall HUI3 scores	Canada
DVT: • PE • EC bleed • IC bleed	Hogg et al. (2013)[40]	215 lower-extremity DVT or PE patients	Standard gamble	Canada
SA: • DVT • PE • EC bleed • IC bleed	Locadia et al. (2004)[44]	124 VTE patients treated with VKA	Time trade-off	Netherlands
Severe PTS (in SA)	Lenert and Soetikno (1997)[41]	30 healthy women between the ages of 20 and 40 years	VAS from scenario describing PTS	US
Post-IC bleed	Rivero-Arias et al. (2010)[42]	The Oxford Vascular Study (population-based cohort; n = 2,425)	EQ-5D	UK
CTEPH (in SA)	Meads et al. (2008)[43]	Pulmonary hypertension patients with CTEPH (n = 308/869)	CAMPHOR QoL	UK

ANCOVA = analysis of covariance; CAMPHOR QoL = Cambridge Pulmonary Hypertension Outcome Review quality of life; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; EQ-5D = EuroQol 5-Dimensions questionnaire; IC = intracranial; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; HUI3 = Health Utilities Index Mark 3; PE = pulmonary embolism; PTS = post-thrombotic syndrome; SA = sensitivity analysis; VAS = visual analogue scale; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Resource Utilization

Drug Costs

Daily drug costs were determined using provincial formulary costs and recommended dosing for the duration of its use (typically 10 days) (Table 13). Some drugs, particularly LMWH, are purchased through hospital formularies at a discount from list price, although the actual price paid is confidential. In order for this analysis to inform the purchasing decisions faced by hospital formularies, we have assumed a 25% discount on the cost of enoxaparin, which has been informally confirmed by hospital pharmacists consulted to approximate the true cost. A range of discounts was used in the sensitivity analysis so that jurisdictions can consider the results that are most applicable to them.

No markup or dispensing fees were applied to drugs (such as UFH and LMWH) administered in the hospital; however, these were applied to medications provided to outpatients (8% and $7, respectively, using costs from Alberta) such as oral warfarin. As UFH is commonly drawn from vials, there is a need to consider the additional daily cost of needles and syringes ($0.54 per administration, administered twice daily).

As there is no known difference in efficacy among LMWHs, only the relative costs of different drugs were considered. These costs are subsumed in the ratio analysis (Table 15) and are not for specific drugs, given that the actual price paid is confidential.

Table 13: Costs of Heparin-Based Therapies to Prevent Venous Thromboembolism

Drug/ Comparator	Strength	Dosage Form	Listing Price ($)	Recommended Daily Use	Average Daily Drug Cost Without Discount ($)	Average Daily Drug Cost, 10% Discount[a] ($)	Average Daily Drug Cost, 25% Discount[a] ($)
Unfractionated Heparins							
Heparin sodium	1,000 IU/ mL	Vial	0.5282	5,000 IU b.i.d.	5.28[b]	NA	NA
Low-Molecular-Weight Heparin							
Enoxaparin sodium (Lovenox)	30 mg/ 0.3 mL 40 mg/ 0.4 mL	Syringe Syringe	6.4870 8.6490	40 mg q.d.	8.65	7.78	6.49
Dalteparin sodium (Fragmin)	2,500 IU 3,500 IU 5,000 IU	Syringe Syringe	5.1657 7.2310 10.3310	5,000 IU q.d.	10.33	NA	NA
Tinzaparin sodium (Innohep)	3,500 IU 4,500 IU	Syringe Syringe	6.0560 7.7880	3,500 IU or 4,500 IU q.d.	6.06 to 7.79	5.45 to 7.01	4.54 to 5.84
Nadroparin calcium[c] (Fraxiparine)	9,500 IU	Syringe	9.1290	2,850 IU q.d.	9.13	8.22	6.85

Drug/ Comparator	Strength	Dosage Form	Listing Price ($)	Recommended Daily Use	Average Daily Drug Cost Without Discount ($)	Average Daily Drug Cost, 10% Discount[a] ($)	Average Daily Drug Cost, 25% Discount[a] ($)
Other Anticoagulants (Treatment of VTE)							
Warfarin (generic)	1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 10 mg	Tablet	0.0780 0.0825 0.0660 0.1023 0.1023 0.0662 0.1187	Usual maintenance: 2 mg to 10 mg daily	0.07 to 0.12	NA	NA

b.i.d. = twice daily; IU = international units; LMWH = low-molecular-weight heparin; NA = not applicable; PE = pulmonary embolism; q.d. = once daily; UFH = unfractionated heparin; VTE = venous thromboembolism.
[a] Consideration provided for potential discounts for LMWH.
[b] Plus additional daily cost of needles and syringes ($1.08 per day for twice-daily administration [$0.54 × 2]).
[c] The only available list price for nadroparin was for the 9,500 IU dose. Flat pricing was assumed. The lower price for the 2,850 IU dose was assessed in sensitivity analysis (including UFH/LMWH cost-ratio analyses).
Source: Alberta Drug Benefit list prices (March 2016), unless otherwise indicated.

Drug Administration

There may be small differences in resource utilization between a once-daily and twice-daily injection. While there is controversy over whether small changes in time result in realized cost savings due to a reduction in health care resources (e.g., nursing time), the model allows for differences in nursing time for administration. The time required for injection of UFH or LMWH and the injection frequencies were obtained from a study from the UK.[45]

Units of Resources by Event

Health care resource utilization for the relevant clinical events in the model by alternate prevention strategy was not reported in the trials from the systematic review. As such, focused literature reviews as well as expert opinion were obtained to determine health care resource utilization for each of the relevant events. Resource use associated with VTE was obtained from a previous economic evaluation and revised to account for the fact that these patients were already hospitalized.

Costs

All costs are reported in 2015 Canadian dollars, detailed in Table 14. Costs were inflated using the Consumer Price Index to 2015.[46] Where appropriate, the unit costs of the resources consumed were obtained from Canadian sources, including the Ontario Case Costing Initiative[47] and Ontario Schedule of Benefits. Literature was used to inform costs of HITT and long-term management costs of PTS and CTEPH (Table 14). Resource use and costs from US sources were converted to 2015 Canadian dollars using the Bank of Canada exchange rate and Consumer Price Index. Unit costs were obtained from Canadian estimates where possible and supplemented by focus literature reviews of relevant costing studies.

Table 14: Cost of Resources Consumed (2015 Canadian Dollars)

Variable Description	Base Estimate ($)	Probability Distribution	Reference
Events			
Prevention administration cost: wage per hour UFH nursing time LMWH nursing time	 32.00 per hour 2.14 per minute 1.13 per minute	 Triangular (± 25%)	 Payscale.com Offord et al. (2004)[45]
HIT: in-patient 1 month of VKA with monitoring cost	5,317 5,193 124	Triangular (± 25%)	 Nanwa et al. (2011)[6] VTE Tx model
HIT with thrombosis (HITT): in-patient 3 months of VKA with monitoring cost	39,138 38,766 372	Triangular (± 25%)	 Nanwa et al.[6] VTE Tx model
Major bleed from prophylaxis: 2 units of blood transfusion 3 extra LOS	4,958 481 1,332 per day		 Amin et al (2004)[48] Cost without insurance
DVT – diagnosis: 1 specialist consultation 1 Doppler ultrasound	453 157 per visit 296 per test	Triangular (± 25%)	 OSB OCCI
DVT – in-patient: 5 days of LMWH 2 extra LOS (2/3 patients) 1 specialist consultation (50% of patients) 3 months of VKA with monitoring cost	2,027 34.60 per day 1,332 per day 157 per visit 372	Triangular (± 25%)	 VTE Tx model Cost without insurance[49] OSB VTE Tx model
PE – diagnosis: 1 specialist consultation 1 ventilation perfusion lung scan (50% of patients) or 1 spiral CT scan (50% of patients)	712 157 per visit 546 per test 564 per test	Triangular (± 25%)	 OSB OCCI
PE – in-patient:[a] 5 days of LMWH 3 extra LOS (2/3 patients) 1 specialist consultation (50% of patients) 3 months of VKA with monitoring cost	4,247 34.60 per day 1,332 per day 157 per visit 372	Triangular (± 25%)	 VTE Tx model Cost without insurance OSB VTE Tx model
CRNM for VTE patients ER visit ER physician fee	391 293 97.60	Triangular (± 25%)	 OCCI OSB
EC bleed (Cost of GI hemorrhage treatment)[b]	5,578	Triangular (± 25%)	OCCI (ICD-10 CA code K922)
IC bleed (acute treatment cost of hemorrhagic stroke: initial hospitalization and follow-up costs)	17,486	Triangular (± 25%)	CADTH; Goeree et al. (2005)[50]
PTS (in SA)	7,522	Triangular (± 25%)	Caprini et al. (2003)[51]
CTEPH (in SA) (PTE surgery: 56.8%)	83,990		Rubens et al. (2007)[52]

Variable Description	Base Estimate ($)	Probability Distribution	Reference
Long-Term Costs (per Annum)			
PTS (in SA) CTEPH (warfarin monitoring + specialist visits) Post-IC bleed	3,300 441 8,338	Triangular (± 25%)	Caprini et al. (2003)[51] OSB CADTH[53]; Goeree et al. (2005)[50]
Monitoring Costs[c]			
INR test INR interpretation and VKA management fee Physician visit	12.31 12.75 77.20	Triangular (± 25%)	BC payment schedule OSB (G271) OSB

BC = British Columbia; CRNM = clinically relevant non-major; CT = computed tomography; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; ER = emergency room; GI = gastrointestinal; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; IC = intracranial; INR = international normalized ratio; LMWH = low-molecular-weight heparin; LOS = length of stay; OCCI = Ontario Case Costing Initiative (2015); OSB = Ontario Schedule of Benefits (2015); PE = pulmonary embolism; PTE = pulmonary thromboendarterectomy; PTS = post-thrombotic syndrome; SA = sensitivity analysis; Tx = treatment; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.
[a] Based on specific code for PE.
[b] As no specific code captures the various types of minor bleeding, the cost is based on the average cost of the 50 most common emergency room visits.
[c] VKA monitoring costs over three months based on three visits to general practitioner, three test interpretations and eight patient tests as assumed in the VTE treatment model.

Sensitivity Analyses

Deterministic Sensitivity Analysis

A wide range of univariate sensitivity analyses was conducted to test the effect of changes in underlying parameter values and assumptions within the models. The parameters tested included the following:

Drug utilization:

- range of discounts potentially realized by hospital formularies for LMWH
- inclusion of time cost to administer injections
- use of alternate LMWH (assuming same discount as enoxaparin)
- increased costs of UFH (cost of UFH has increased over time).

Cohort:

- medical cohort by stroke versus no stroke
- surgical patients with cancer.

Baseline probabilities:

- upper and lower ranges of variance for each parameter
- surgical cohort by cancer versus no cancer.

Efficacy:

- point estimate and range of 95% CI (from clinical review).

Additional Scenario Analysis

A series of scenario analyses was also conducted, focusing on resource utilization for the index VTE event as well as monitoring. These included:

- using a lifetime time horizon
- inclusion of health states of PTS and CTEPH (same probability of occurrence as per treatment report)
- HITT scenario (see below)
- ratio analysis considering alternate ratios of the cost of UFH to LMWH (see below).

HITT Scenario

HIT alone or with thrombosis (HITT) was not assessed in the clinical systematic review, as it was not an outcome reported in the included studies. However, it is an important clinical outcome, and there are data to suggest that LMWH is associated with a lower risk of HITT than UFH.[21,32] Clinical experts indicated that inclusion of HITT is a critical component of this model. As such, a HITT scenario was to account for this event and its consequences in both surgical and medical patients, including sensitivity analysis within this scenario.

Ratio Analysis

There is variability in the actual price paid for various LMWH and UFH products by institution and jurisdiction, influenced by price factors (confidentiality agreements, volume-based pricing, change in price over time), product packaging (vials versus pre-filled syringes), and additional pharmacy costs (preparing syringes). The actual costs (and variability) cannot be accurately ascertained due to the confidential nature of pricing agreements, and further changes in price may occur over time.

A ratio analysis was conducted to provide analyses that reflect current and future relative pricing. The reference-case LMWH and UFH costs were used as an anchor, and a range of the ratio of UFH/LMWH costs was assessed (Box 1 and Table 15). This allows end users to identify the likely cost scenario at their institution (applicable even if the "anchored" cost varies, as the difference in cost that most closely represents the reality in the jurisdiction can be used). Exploration of the range of the ratio may also identify "thresholds," at which point conclusions change. Three hospital pharmacy sources verified that the true differences in cost between UFH and LMWH would be captured in the range assessed.

Box 1: Approach to Ratio Calculation

Ratio Analysis

Ratio UFH = daily cost UFH (5,000 IU) ÷ daily cost enoxaparin (40 mg) with 25% discount
= (2.641 × 2) ÷ 6.487 = 0.814 (base case)

Daily cost of LMWH = 8.649 × 0.75 = 6.487

Daily cost of UFH = (Ratio UFH × daily cost LMWH) + (2 × cost of syringe)
= (0.814 × 6.487) + (2 × 0.54)
= 6.362

IU = international units; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

Table 15: Ratio Analysis of Cost of Unfractionated Heparin and Low-Molecular-Weight Heparin

Ratio	Daily LMWH Cost ($)	Daily UFH Cost ($) (Excluding Cost of Syringe)	Incremental Daily Cost ($)
Reference case 0.814	**6.487**[a]	**5.282**[b]	**1.205**
Ratio decreased to 0.10	6.487	0.649	5.838
Ratio decreased to 0.20	6.487	1.297	5.190
Ratio decreased to 0.30	6.487	1.946	4.541
Ratio decreased to 0.40	6.487	2.595	3.892
Ratio decreased to 0.50	6.487	3.244[c]	3.243
Ratio decreased to 0.60	6.487	3.892	2.595
Ratio decreased to 0.70	6.487	4.541	1.946
Ratio decreased to 0.80	6.487	5.190	1.297
Ratio increased to 0.90	6.487	5.838	0.649
Ratio increased to 1.00	6.487	6.487	0

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.
Note: The ratio considers the acquisition cost of UFH only; the cost of syringes is added to this cost. As in the reference case, cost of preparation and administration are not included (examined in sensitivity analysis in the reference case).
[a] Represents a 25% reduction in the list price of enoxaparin (Alberta).
[b] List price of UFH provincial formulary (not hospital formulary) (Alberta).
[c] Plausible cost of UFH reported in some jurisdictions.

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis was conducted using a Monte Carlo simulation. For the simulation, probability distributions related to natural history parameters, hazard ratios, resource utilization (costs), and utilities were incorporated into the analysis.

This analysis adopted standard methods for defining uncertainty around parameters. Transition probabilities were characterized by beta and normal distributions and RRs, and ORs were characterized by lognormal distributions. Utility decrements were characterized by normal distributions.

Estimates of incremental costs and QALYs were obtained by rerunning the model employing values from the related probability distributions. In this study, 10,000 replications were conducted — i.e., a set of 10,000 outcome estimates was obtained. Cost-effectiveness acceptability

curves were derived that present the probability that each treatment is optimal, given different values of willingness to pay for an additional QALY.

Model Validation

Adhering to best practices for conducting economic evaluations,[3] before analyzing the results of the economic model, ensured the results were logically plausible and could be explained intuitively. The model was also assessed for logical inconsistencies by evaluating it under hypothetical conditions. The mathematical calculations were confirmed to be accurate and consistent with the specifications of the model (internal validity). It was determined that the model had predictive validity by comparing model outputs (a function of input variables and model structure) with outcomes from studies in the systematic review.

Model validation results are shown in Table 16 and Table 17. Internal validity is demonstrated by comparing model-predicted values with the informing estimates.

Table 16: Model Validation — Input and Output Values for Unfractionated Heparin Strategy — Surgical Patients

Variable Description	Literature/NMA Estimate	Lower 95% CI (Min)	Upper 95% CI (Max)	Reference	Model-Predicted Value
Probability of any VTE	0.0159	0.0012	0.0247	Weighted average of observational studies	0.0145 to 0.0168
Probability of HIT	0.02	0.02	0.0291	Expert opinion; Junqueira et al.[21]	0.0183 to 0.0203
Probability of any bleed from prophylaxis	0.0653	-	-	NMA	0.0658 to 0.0686
Probability of major bleed from prophylaxis	(0.065 × 0.25) 0.01625	0.013	0.099	NMA; observational studies	0.0158 to 0.0171

CI = confidence interval; HIT = heparin-induced thrombocytopenia; NMA = network meta-analysis; VTE = venous thromboembolism.

Table 17: Model Validation — Input and Output Values for Unfractionated Heparin Strategy— Medical Patients

Variable Description	Literature/NMA Estimate	Lower 95% CI (Min)	Upper 95% CI (Max)	Reference	Model-Predicted Value
Probability of any VTE	0.007	0.0015	0.012	Weighted average of observational studies	0.0059 to 0.0074
Probability of HIT	0.01	0.0002	0.027	Expert opinion; Leykum et al.[7]; Rothberg et al.[26]	0.0091 to 0.0098
Probability of any bleed from prophylaxis	0.0628	-	-	NMA	0.0617 to 0.0633
Probability of major bleed from prophylaxis	(0.0628 × 0.107) 0.00672	0.0026	0.016	NMA; observational studies	0.0044 to 0.0075

CI = confidence interval; HIT = heparin-induced thrombocytopenia; NMA = network meta-analysis; VTE = venous thromboembolism.

Results

Surgical Patients: Reference Case

The incremental cost and cost-effectiveness of VTE prevention is presented in Table 18, with disaggregated costs in Table 19. Compared with UFH, LMWH was associated with an incremental cost of $59.54 and the same effectiveness over a three-month time horizon; thus, UFH is the preferred strategy. The difference in cost was driven primarily by the increased occurrence and attendant cost of major bleeding associated with LMWH, in addition to the slightly higher drug acquisition cost of LMWH.

Table 18: Reference Case Results — Surgical Patients

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
UFH	563.08	-	0.30599	-	-
LMWH	622.62	59.54	0.30599	0	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

Table 19: Reference Case Disaggregated Costs ($) — Surgical Patients

Strategy	Ten-Day Drug Cost	Bleeding Cost From Prophylaxis	HIT Cost	VTE Cost
UFH	63.61	80.96	338.87	79.64
LMWH	64.85	139.26	338.87	79.64

HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

The results are similar when a lifetime horizon is used (with and without incorporation of long-term outcomes of CTEPH, PTS, and recurrent VTE) as shown in Table 20 to Table 23.

Table 20: Lifetime Horizon Results — Surgical Patients

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
UFH	565.51	-	14.245	-	-
LMWH	625.05	59.54	14.245	0	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

Table 21: Lifetime Horizon Disaggregated Costs ($) — Surgical Patients

Strategy	Ten-Day Drug Cost	Bleeding Cost from Prophylaxis	HIT Cost	VTE Cost
UFH	63.61	80.96	338.87	82.07
LMWH	64.85	139.26	338.87	82.07

HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 22: Lifetime Horizon With Long-Term Outcomes (CTEPH, PTS, rVTE) — Surgical Patients

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
UFH	634.71	-	14.173	-	-
LMWH	694.25	59.54	14.173	0	Dominated

CTEPH = chronic thromboembolic pulmonary hypertension; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; PTS = post-thrombotic syndrome; QALY = quality-adjusted life-year; rVTE = recurrent venous thromboembolism; UFH = unfractionated heparin.

Deterministic Sensitivity Analysis: Surgical Patients

When a discount rate of 0% to 3% was used, there were no changes in the conclusions of the model: LMWH remained associated with similar QALYs but greater costs compared with UFH (full results not shown; includes analyses using a lifetime time horizon).

Table 23 shows the results of the sensitivity analysis with a range of discounts applied to the cost of LMWH, as well as the cost of alternate LMWH products. LMWH remained dominated by UFH in all analyses.

Table 23: Sensitivity Analysis of Drug Costs — Surgical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case LMWH (25% discount)	59.54	0	Dominated
No discount with LMWH LMWH	81.16	0	Dominated
LMWH costs reduced by 5% LMWH	76.84	0	Dominated
LMWH costs reduced by 10% LMWH	72.51	0	Dominated
LMWH costs reduced by 15% LMWH	68.19	0	Dominated

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
LMWH costs reduced by 20% LMWH	63.87	0	Dominated
LMWH costs reduced by 30% LMWH	55.22	0	Dominated
LMWH costs reduced by 35% LMWH	50.89	0	Dominated
LMWH costs reduced by 40% LMWH	46.57	0	Dominated
LMWH costs reduced by 45% LMWH	42.24	0	Dominated
LMWH costs reduced by 50% LMWH	37.92	0	Dominated
Cost of tinzaparin $4.542 with 25% discount LMWH	40.09	0	Dominated
Cost of nadroparin $6.847 with 25% discount LMWH	63.14	0	Dominated
Cost of dalteparin $7.7475 with 25% discount LMWH	72.15	0	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year.

As the OR of bleeding from prophylaxis is higher with LMWH in non-orthopedic surgical patients, assumptions on bleeding from prophylaxis were tested in the sensitivity analysis. The reference case assumptions are shown in Box 2, and the results of the variables tested in the sensitivity analysis are listed in Table 24. The incremental cost of LMWH compared with UFH varied; however, reference-case conclusions were unaltered. While, a priori, the relative risk (RR) of "any bleed" was used in the reference case (and was statistically significant), when broken out by major and minor bleeding, major bleeding was not statistically significant (OR, 1.70; 95% CI, 0.82 to 3.92), while minor bleeding was significant (OR, 1.65; 95% CI, 1.05 to 2.60). When 1.0 and 1.65 were used for major and minor bleeding, respectively, conclusions were unchanged, although the incremental cost was very small ($1.25).

Box 2: Reference Case Parameters for Bleeding — Surgical Patients

Bleed From Prophylaxis

Baseline risk = 42 ÷ 643 = 6.53%. OR = 1.72 (1.15 to 2.56)

- minor bleed
  - proportion of minor bleed = 1 – proportion of major bleed = 75%
  - assumed no additional cost
  - assumed no QALY change
- major bleed
  - proportion of major bleed = 28 ÷ 112 = 25% (NMA)
  - assumed additional 3 LOS and two units of transfusion
    - additional cost of $4,958
  - assumed no change in quality of life.

LOS = length of stay; NMA = network meta-analysis; OR = odds ratio; QALY = quality-adjusted life-year.

Table 24: Sensitivity Analysis on Bleeding Parameters — Surgical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case LMWH	59.54	0	Dominated
7 days of prophylaxis LMWH	59.17	0	Dominated
UFH 5,000 IU t.i.d. LMWH	27.73	0	Dominated
Nursing time (LMWH, $0.603; UFH, $1.141) LMWH	42.75	0	Dominated
OR of bleed from prophylaxis; lower CI, 1.15 LMWH	13.39	0	Dominated
OR of bleed from prophylaxis; upper CI, 2.56 LMWH	127.55	0	Dominated
OR of major bleed, 1; OR of minor bleed, 1.65 LMWH	1.25	0	Dominated
1 LOS for major bleed LMWH	28.22	0	Dominated
2 LOS for major bleed LMWH	43.88	0	Dominated
0 unit transfusion for major bleed LMWH	48.23	0	Dominated
1 unit transfusion for major bleed LMWH	53.89	0	Dominated
Baseline risk decreased by 25% LMWH	44.97	0	Dominated
Baseline risk decreased by 50% LMWH	30.39	0	Dominated
Baseline risk increased by 25% LMWH	74.11	0	Dominated
Baseline risk increased by 50% LMWH	88.69	0	Dominated

CI = confidence interval; ICUR = incremental cost-utility ratio; IU = international units; LMWH = low-molecular-weight heparin; LOS = length of stay; OR = odds ratio; QALY = quality-adjusted life-year; t.i.d. = three times daily; UFH = unfractionated heparin.

A sensitivity analysis was also conducted on parameters relevant to VTE, including the extremes of the 95% CI of the OR as well as other parameters and assumptions on VTE. As shown in Table 25, UFH remained the preferred strategy, except when the lower CI of the RR of VTE was used, at which point LMWH became more effective and remained more costly, with an incremental cost-utility ratio of $500,005 per QALY.

Table 25: Sensitivity Analysis of Venous Thromboembolism — Surgical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case LMWH	59.54	0	Dominated
OR of VTE; lower CI, 0.64 LMWH	32.67	0.0000653	500,005
OR of VTE; upper CI, 1.55 LMWH	100.59	–0.0000998	Dominated
Proportion of DVT from treatment model; 0.57 LMWH	59.54	0	Dominated
DOAC VTE (APX/RIV/DAB) LMWH	59.54	0	Dominated

APX = apixaban; CI = confidence interval; DAB = dabigatran; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; OR = odds ratio; QALY = quality-adjusted life-year; RIV = rivaroxaban; VTE = venous thromboembolism.

Finally, a scenario analysis on the ratio of the cost of UFH and LMWH was conducted, with results presented in Table 26. LMWH remained dominated by UFH over the range of ratio of costs from 0.10 to 1.00 (reference value: 0.814).

Table 26: Ratio Analysis — Surgical Patients Reference Case

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case (ratio = 0.814) LMWH	**59.54**	**0**	**Dominated**
Ratio decreased to 0.10 LMWH	105.87	0	Dominated
Ratio decreased to 0.20 LMWH	99.39	0	Dominated
Ratio decreased to 0.30 LMWH	92.90	0	Dominated
Ratio decreased to 0.40 LMWH	86.41	0	Dominated
Ratio decreased to 0.50 LMWH	79.93	0	Dominated
Ratio decreased to 0.60 LMWH	73.44	0	Dominated
Ratio decreased to 0.70 LMWH	66.95	0	Dominated
Ratio decreased to 0.80 LMWH	60.47	0	Dominated
Ratio increased to 0.90 LMWH	53.98	0	Dominated
Ratio increased to 1.00 LMWH	47.49	0	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year.

HITT Scenario Analysis: Surgical Patients

Plausible parameters for the HITT scenario in surgical patients were identified through literature review and by clinical experts (Table 4 and Table 14) and are summarized in Box 3. The sensitivity analysis conducted on this scenario incorporated alternate literature sources on the baseline probability and OR/RR of HITT from alternate sources. Further, a (lower-quality) reference[5] that suggests lower costs attributable to HITT was examined, and a sensitivity analysis on bleeding probability and consequences was considered.

Box 3: HIT Scenario — Non-Orthopedic Surgical Patients

HIT

Baseline risk: 0.02 with UFH (0.00165 to 0.0291)
HIT OR (LMWH vs. UFH) from Martel et al.[32]: 0.1 (0.01 to 0.82)
RR from Junqueira et al.[21]: 0.24 (0.07 to 0.82)

Without thrombosis (HIT):

- proportion of HIT: 1 – proportion of HITT = 65%
- cost of HIT: $5,193 base case (Nanwa et al.[6])
  - SA: $1,489 (McGarry et al.[5])
- susceptible to bleeding from HIT treatment (assumed same as VTE treatment):
  - baseline probability 0.0164
  - can be CRNM or major (IC/EC)
  - other probabilities, costs, and QALYs are assumed to be the same as VTE.

With thrombosis (HITT):

- proportion of HITT: 35% (expert opinion)
- cost of HITT: $38,766 base case (Nanwa et al.[6])
  - SA: $10,550 (McGarry et al.[5])
  - also assumed additional 3 months of VKA treatment ($372)
- also susceptible to bleeding (assumed same as VTE treatment)
  - baseline probability 0.0164
  - can be CRNM or major (IC/EC)
  - other probabilities, costs, and QALYs are assumed to be the same as VTE.
- probability of mortality: 8%.

CRNM = clinically relevant non-major; EC = extracranial; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; IC = intracranial; LMWH = low-molecular-weight heparin; OR = odds ratio; QALY = quality-adjusted life-year; RR = relative risk; SA = sensitivity analysis; UFH = unfractionated heparin; VKA = vitamin K antagonist; vs. = versus; VTE = venous thromboembolism.

In the HITT scenario and sensitivity analysis of surgical patients (Table 27) where the risk of HITT is lower for LMWH compared with UFH, LMWH was less costly and resulted in greater QALYs, although the incremental difference in quality of life was very small. When the probability of HIT was very low (0.00165), LMWH was slightly more costly and resulted in slightly more QALYs than UFH, with very large ICURs (which is due to dividing the small incremental cost by a very small incremental QALY).

Table 27: HITT Scenario Analysis and Sensitivity Analysis — Surgical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case UFH	249.93	–0.0001498	Dominated
UFH 5,000 IU t.i.d. UFH	281.74	–0.0001498	Dominated
OR of HIT (Martel et al.[32]), lower CI, 0.01 UFH	280.88	–0.0001648	Dominated
OR of HIT (Martel et al.[32]), upper CI, 0.82 UFH	2.35	–0.0000300	Dominated

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
RR of HIT (Junqueira et al.[21]), 0.24 UFH	201.79	–0.0001265	Dominated
RR of HIT (Junqueira et al.[21]), lower CI, 0.07 UFH	260.25	–0.0001548	Dominated
RR of HIT (Junqueira et al.[21]), upper CI, 0.82 UFH	2.35	–0.0000300	Dominated
Probability of HIT (suspected) (McGowan et al.[31]), 0.00855 UFH	72.76	–0.0000640	Dominated
Probability of HIT (suspected) (McGowan et al.[31]), 0.00855 UFH vs. 0.0049 LMWH (RR, 0.573) UFH	3.21	–0.0000304	Dominated
Probability of HIT (positive), 0.00165 (McGowan et al.[31]) LMWH	34.01	0.0000124	2,751,778
Probability of HIT (positive), 0.00165 UFH vs. 0.00061 LMWH (RR, 0.37) (McGowan et al.[31]) LMWH	41.66	0.0000087	4,813,153
Probability of HIT, upper CI, 0.291 (Junqueira et al.[21]) UFH	390.74	–0.0002180	Dominated
Proportion of HITT, 43% vs. 19% (McGowan et al.[31]) UFH	314.95	–0.0001949	Dominated
Proportion of HITT, 78.6% vs. 66.7% (Junqueira et al.[21]) UFH	523.77	–0.0003399	Dominated
HIT cost: $1,489; HITT cost: $10,550 (McGarry et al.[5]) UFH	28.83	–0.0001498	Dominated
0% probability of bleed from HIT/HITT treatment UFH	249.24	–0.0001544	Dominated
1 LOS for major bleed UFH	281.25	–0.0001498	Dominated
2 LOS for major bleed UFH	265.59	–0.0001498	Dominated
0 unit transfusion for major bleed UFH	261.24	–0.0001498	Dominated
1 unit transfusion for major bleed UFH	255.59	–0.0001498	Dominated
OR of major bleed, 1; OR of minor bleed, 1.65 UFH	308.22	–0.0001498	Dominated
Probability of bleed from prophylaxis decreased by 25% UFH	264.50	–0.0001498	Dominated
Probability of bleed decreased by 50% UFH	279.08	–0.0001498	Dominated
Probability of bleed increased by 25% UFH	235.36	–0.0001498	Dominated

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Probability of bleed increased by 50% UFH	220.78	–0.0001498	Dominated
VTE treated with DOAC (APX/RIV/DAB) UFH	249.93	–0.0001498	Dominated

APX = apixaban; CI = confidence interval; DAB = dabigatran; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; LOS = length of stay; OR = odds ratio; QALY = quality-adjusted life-year; RIV = rivaroxaban; RR = relative risk; UFH = unfractionated heparin; vs. = versus; VTE = venous thromboembolism.

The ratio analysis was also applied to the HITT scenario reference case in surgical patients. Over a range of cost ratios for UFH versus LMWH (Table 28) on the surgical patient HITT scenario reference case (Table 27), the ratio of costs of UFH and LMWH was assessed, and UFH remained dominated over the range of ratios.

Table 28: Ratio Analysis of HITT Scenario — Surgical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case (ratio = 0.814) UFH	249.93	–0.0001498	Dominated
Ratio decreased to 0.10 UFH	203.60	–0.0001498	Dominated
Ratio decreased to 0.20 UFH	210.08	–0.0001498	Dominated
Ratio decreased to 0.30 UFH	216.57	–0.0001498	Dominated
Ratio decreased to 0.40 UFH	223.06	–0.0001498	Dominated
Ratio decreased to 0.50 UFH	229.54	–0.0001498	Dominated
Ratio decreased to 0.60 UFH	236.03	–0.0001498	Dominated
Ratio decreased to 0.70 UFH	242.52	–0.0001498	Dominated
Ratio decreased to 0.80 UFH	249.01	–0.0001498	Dominated
Ratio increased to 0.90 UFH	255.49	–0.0001498	Dominated
Ratio increased to 1.00 UFH	261.98	–0.0001498	Dominated

HITT = heparin-induced thrombocytopenia and thrombosis; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

Subgroup Analysis: Non-Orthopedic Surgical Patients With Cancer

The subgroup analyses on surgical patients with cancer are presented in Table 29 and Table 30. Since the OR for both UFH and LMWH is 1 (no difference in either VTE or bleeding), UFH is the preferred strategy, as the cost is lower when the effectiveness of the two drugs is the same. It should be noted that the cost differences are very small and are due to drug acquisition costs.

Table 29: Reference Case Results — Surgical Patients With Cancer

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
UFH	588.97	-	0.30606	–	–
LMWH	590.22	1.25	0.30606	0	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

Table 30: Disaggregated Costs ($) — Surgical Patients With Cancer

Strategy	Ten-Day Drug Cost	Bleeding Cost From Prophylaxis	HIT Cost	VTE Cost
UFH	63.61	122.14	338.87	64.36
LMWH	64.85	122.14	338.87	64.36

HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

The HITT scenario was also examined in this subgroup of surgical patients, with results in Table 31. In all circumstances, LMWH was less costly and more effective than UFH.

Table 31: HITT Scenario and Sensitivity Analysis — Surgical Patients With Cancer

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case UFH	308.22	–0.0001498	Dominated
UFH 5,000 IU t.i.d. UFH	340.03	–0.0001498	Dominated
OR of HIT (Martel et al.[32]), lower CI, 0.01 UFH	339.17	–0.0001648	Dominated
OR of HIT, upper CI, 0.82 UFH	60.65	–0.0000300	Dominated
RR of HIT (Junqueira et al.[21]), 0.24 UFH	260.08	–0.0001265	Dominated
RR of HIT, lower CI, 0.07 UFH	318.54	–0.0001548	Dominated
RR of HIT, upper CI, 0.82 UFH	60.65	–0.0000300	Dominated
Risk of HIT (suspected), 0.00855 (McGowan et al.[31]) UFH	131.05	–0.0000640	Dominated

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Risk of HIT (suspected), 0.00855 vs. 0.0049 (RR, 0.573) UFH	61.51	–0.0000304	Dominated
Risk of HIT (positive), 0.00165 UFH	24.28	–0.0000124	Dominated
Risk of HIT (positive), 0.00165 vs. 0.00061 (RR, 0.37) UFH	16.63	–0.0000087	Dominated
Risk of HIT upper CI, 0.291 UFH	449.03	–0.0002180	Dominated
Proportion of HITT, 43% vs. 19% (McGowan et al.) UFH	373.25	–0.0001949	Dominated
Proportion of HITT, 78.6% vs. 66.7% (Junqueira et al.[21]) UFH	582.06	–0.0003399	Dominated
HIT cost, $1,489; HITT cost, $10,550 (McGarry et al.[5]) UFH	87.13	–0.0001498	Dominated
DOAC VTE (APX/RIV/DAB) UFH	308.22	–0.0001498	Dominated

APX = apixaban; CI = confidence interval; DAB = dabigatran; DOAC = direct oral anticoagulant; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RIV = rivaroxaban; RR = relative risk; UFH = unfractionated heparin; vs. = versus; VTE = venous thromboembolism.

Medical Patients: Reference Case

The incremental cost and cost-effectiveness of VTE prevention in medical patients is presented in Table 32. Compared with UFH, LMWH is associated with a small cost saving of $9.27, and slightly more incremental QALYs of 0.0000108 over the three-month time horizon; thus, LMWH is dominant compared with UFH. The major driver of cost savings is reduced costs of VTE (Table 33), which also lead to the slight QALY gain. The model results are also unchanged in the long-term models, with or without inclusion of long-term outcomes of PTS, CTEPH, and recurrent VTE (Table 34 to Table 36).

Table 32: Reference Case Results — Medical Patients

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH	280.46	-	0.30617	-	-
UFH	289.73	9.27	0.30615	–0.0000108	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

Table 33: Reference Case Disaggregated Costs ($) — Medical Patients

Strategy	Ten-Day Drug Cost	Bleeding Cost From Prophylaxis	HIT Cost	VTE Cost
LMWH	64.86	33.15	169.44	13.01
UFH	63.61	33.15	169.44	23.53

HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 34: Lifetime Model Results — Medical Patients

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH	281.16	-	9.689	-	-
UFH	290.69	9.53	9.688	–0.0011227	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 35: Lifetime Model Disaggregated Costs ($) — Medical Patients

Strategy	Ten-Day Drug Cost	Bleeding Cost From Prophylaxis	HIT Cost	VTE Cost
LMWH	64.86	33.15	169.44	13.71
UFH	63.61	33.15	169.44	24.49

HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 36: Lifetime Model With Long-Term Outcomes (CTEPH, PTS, rVTE) — Medical Patients

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH	293.06	-	9.678	-	-
UFH	314.48	21.43	9.665	–0.0129762	Dominated

CTEPH = chronic thromboembolic pulmonary hypertension; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; PTS = post-thrombotic syndrome; QALY = quality-adjusted life-year; rVTE = recurrent venous thromboembolism; UFH = unfractionated heparin.

Deterministic Sensitivity Analysis — Medical Patients

When a discount rate of 0% to 3% was used, there were no changes in the conclusions of the model, with UFH associated with slightly greater costs and slightly lower QALYs compared with LMWH (results not shown).

Table 37 shows the results of a sensitivity analysis when a range of discounts is applied to the cost of LMWH and explores the costs of alternate LMWH products. LMWH was more expensive and more effective than UFH when the discount realized by hospital formularies was 10% or less (compared with the discount rate of 25% used in the reference case), or when dalteparin was used instead of enoxaparin, resulting in ICURs of $300,000 to $1 million per QALY. The very high ICURs are observed because the small cost differences are divided by a very small incremental QALY.

Table 37: Sensitivity Analysis on Drug Costs — Medical Patients

Sensitivity Analysis	Incremental Cost	Incremental QALY	ICUR ($/QALY)
Reference case UFH (25% discount)	9.27	–0.0000108	Dominated
No discount with LMWH LMWH	12.36	0.0000108	1,143,736
LMWH costs reduced by 5% LMWH	8.03	0.0000108	743,460
LMWH costs reduced by 10% LMWH	3.71	0.0000108	343,183
LMWH costs reduced by 15% UFH	0.62	–0.0000108	Dominated
LMWH costs reduced by 20% UFH	4.94	–0.0000108	Dominated
LMWH costs reduced by 30% UFH	13.59	–0.0000108	Dominated
LMWH costs reduced by 35% UFH	17.91	–0.0000108	Dominated
LMWH costs reduced by 40% UFH	22.24	–0.0000108	Dominated
LMWH costs reduced by 45% UFH	26.56	–0.0000108	Dominated
LMWH costs reduced by 50% UFH	30.89	–0.0000108	Dominated
Cost of tinzaparin $4.542 with 25% discount UFH	28.71	–0.0000108	Dominated
Cost of nadroparin $6.847 with 25% discount UFH	5.66	–0.0000108	Dominated
Cost of dalteparin $7.7475 with 25% discount LMWH	3.34	0.0000108	309,306

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

The impact of the relative cost of UFH and LMWH was further examined in a scenario analysis that considered the ratio of the cost of the two drugs, and the ratio of the cost in the reference case at 0.814 (Table 38). The LMWH strategy becomes more costly when the ratio is 0.60 ($6.40 for LMWH versus ≤ $3.89 for UFH, a cost difference of $2.51), and again produces very large ICURs due to the very small incremental difference in QALYs.

Table 38: Ratio Analysis in Reference Case — Medical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case (ratio = 0.814) UFH	9.27	–0.0000108	Dominated
Ratio decreased to 0.10 LMWH	37.07	0.0000108	3,430,969
Ratio decreased to 0.20 LMWH	30.58	0.0000108	2,830,554
Ratio decreased to 0.30 LMWH	24.09	0.0000108	2,230,139

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Ratio decreased to 0.40 LMWH	17.61	0.0000108	1,629,724
Ratio decreased to 0.50 LMWH	11.12	0.0000108	1,029,309
Ratio decreased to 0.60 LMWH	4.63	0.0000108	428,894
Ratio decreased to 0.70 UFH	1.85	–0.0000108	Dominated
Ratio decreased to 0.80 UFH	8.34	–0.0000108	Dominated
Ratio increased to 0.90 UFH	14.83	–0.0000108	Dominated
Ratio increased to 1.00 UFH	21.31	–0.0000108	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

Table 39 and Table 40 present the results of a sensitivity analysis on prevention parameters and VTE assumption. LMWH was the preferred (dominant) strategy under different prophylaxis and VTE assumptions, except when the upper CI of the RR of bleeding from prophylaxis was used. In that case, LMWH was more expensive and more effective, resulting in an incremental cost-utility ratio of $185,621 per QALY.

Table 39: Sensitivity Analysis on Prevention Assumptions — Medical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case UFH	9.27	–0.0000108	Dominated
Seven days of prophylaxis UFH	9.64	–0.0000108	Dominated
UFH: 5,000 IU t.i.d. UFH	41.08	–0.0000108	Dominated
Nursing time: LMWH, $0.603; UFH, $1.141 UFH	26.06	–0.0000108	Dominated
OR of bleed from prophylaxis: lower CI, 0.71 UFH	18.88	–0.0000108	Dominated
OR of bleed from prophylaxis: upper CI, 1.34 LMWH	2.01	0.0000108	185,621

CI = confidence interval; ICUR = incremental cost-utility ratio; IU = international units; LMWH = low-molecular-weight heparin; OR = odds ratio; QALY = quality-adjusted life-year; t.i.d. = three times daily; UFH = unfractionated heparin.

Table 40: Sensitivity Analysis on Venous Thromboembolism Assumptions — Medical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case UFH	9.27	–0.0000108	Dominated
OR of VTE: lower CI, 0.37 UFH	12.00	–0.0000136	Dominated
OR of VTE: upper CI, 0.67 UFH	5.69	–0.0000071	Dominated
Proportion of DVT from treatment model, 0.57 UFH	12.70	–0.0000276	Dominated
DOAC VTE (APX/RIV/DAB) UFH	9.92 to 9.99	–0.0000108	Dominated

APX = apixaban; CI = confidence interval; DAB = dabigatran; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; ICUR = incremental cost-utility ratio; OR = odds ratio; QALY = quality-adjusted life-year; RIV = rivaroxaban; UFH = unfractionated heparin; VTE = venous thromboembolism.

Heparin-Induced Thrombocytopenia and Thrombosis Scenario Analysis – Medical Patients

Plausible parameters for the HITT scenario in medical patients were identified through literature review and by clinical experts (Table 4 and Table 14) and are summarized in Box 4. The sensitivity analysis conducted on this scenario incorporated alternate literature sources on the baseline probability and RR of HITT from alternate sources. Further, a (lower-quality) reference[5] that suggests lower costs attributable to HITT was examined, and a sensitivity analysis on bleeding probability and consequences was considered.

Box 4: HITT Scenario — Medical Patients

HIT

Baseline risk: 0.01 with UFH (0.0002 to 0.027)
HIT OR (LMWH vs. UFH) from Martel et al.[32]: 0.1 (0.01 to 0.82)
RR from Junqueira et al.[21]: 0.24 (0.07 to 0.82)

Without thrombosis:

- proportion of HIT: 1 minus proportion of HITT = 65%
- cost of HIT: $5,193 base case (Nanwa et al.[6])
  - SA: $1,489 (McGarry et al.[5])
- susceptible to bleeding from HIT treatment (assumed same rate as VTE treatment = 0.0164)
  - can be CRNM, major (IC/EC)
  - probabilities, costs, and QALYs are assumed to be the same as VTE.

With thrombosis:

- proportion of HITT: 35% (expert opinion)
- cost of HITT: $38,766 base case (Nanwa et al.[6])
  - SA: $10,550 (McGarry et al.[5])
  - also assumed additional 3 months of VKA treatment ($372)
- also susceptible to bleeding (assumed same as VTE treatment)
- probability of mortality: 8%.

CRNM = clinically relevant non-major; EC = extracranial; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; IC = intracranial; QALY = quality-adjusted life-year; SA = sensitivity analysis; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

In the HITT scenario reference case, as well as in the sensitivity analysis conducted on this scenario, LMWH was associated with lower costs and greater QALYs compared with UFH (Table 41). This conclusion was unchanged over a range of relative costs of UFH versus LMWH in ratio analysis (Table 42).

Table 41: HITT Scenario and Sensitivity Analysis — Medical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case UFH	164.00	–0.0000857	Dominated
UFH, 5,000 IU t.i.d. UFH	195.81	–0.0000857	Dominated
OR of HIT (Martel et al.[32]), lower CI, 0.01 UFH	179.48	–0.0000932	Dominated
OR of HIT (Martel et al.[32]), upper CI, 0.82 UFH	40.21	–0.0000258	Dominated
RR of HIT (Junqueira et al.[21]), 0.24 UFH	139.93	–0.0000740	Dominated
RR of HIT (Junqueira et al.[21]), lower CI, 0.07 UFH	169.16	–0.0000882	Dominated
RR of HIT (Junqueira et al.[21]), upper CI, 0.82 UFH	40.21	–0.0000258	Dominated
Probability of HIT (suspected), 0.00855 (McGowan et al.[31]) UFH	141.56	–0.0000748	Dominated

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Probability of HIT (suspected), 0.00855 vs. 0.0049 (RR, 0.573) (McGowan et al.[31]) UFH	72.02	–0.0000412	Dominated
Probability of HIT (positive), 0.00165 (McGowan et al.[31]) UFH	34.80	–0.0000232	Dominated
Probability of HIT (positive), 0.00165 vs. 0.00061 (RR, 0.37) (McGowan et al.[31]) UFH	27.15	–0.0000195	Dominated
Probability of HIT, lower CI, 0.0002 (Rothberg et al.[26]) UFH	12.36	–0.0000123	Dominated
Probability of HIT, upper CI, 0.027 (Leykum et al.[7]) UFH	427.05	–0.0002129	Dominated
Proportion of HITT, 43% vs. 19% (McGowan et al.[31]) UFH	196.51	–0.0001082	Dominated
Proportion of HITT, lower CI, 40% UFH	179.24	–0.0000963	Dominated
Proportion of HITT, upper CI, 54.3% UFH	222.83	–0.0001265	Dominated
HIT cost, $1,489; HITT cost, $10,550 (McGarry et al.[5]) UFH	53.45	–0.0000857	Dominated
DOAC VTE (APX/RIV/DAB) UFH	164.66 to 164.72	–0.0000857	Dominated

APX = apixaban; CI = confidence interval; DAB = dabigatran; DOAC = direct oral anticoagulant; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; ICUR = incremental cost-utility ratio; OR = odds ratio; QALY = quality-adjusted life year; RIV = rivaroxaban; RR = relative risk; UFH = unfractionated heparin; vs. = versus; VTE = venous thromboembolism.

The ratio analysis was also applied to the HITT scenario reference case in medical patients. The model conclusions were unaltered over the range of cost ratios examined (Table 42).

Table 42: Ratio Analysis of HITT Scenario — Medical Patients

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case (ratio = 0.814) UFH	164.00	−0.0000857	Dominated
Ratio decreased to 0.10 UFH	117.67	−0.0000857	Dominated
Ratio decreased to 0.20 UFH	124.16	−0.0000857	Dominated
Ratio decreased to 0.30 UFH	130.64	−0.0000857	Dominated
Ratio decreased to 0.40 UFH	137.13	–0.0000857	Dominated
Ratio decreased to 0.50 UFH	143.62	−0.0000857	Dominated
Ratio decreased to 0.60 UFH	150.10	−0.0000857	Dominated
Ratio decreased to 0.70 UFH	156.59	−0.0000857	Dominated
Ratio decreased to 0.80 UFH	163.08	−0.0000857	Dominated
Ratio increased to 0.90 UFH	169.56	−0.0000857	Dominated

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Ratio increased to 1.00 UFH	176.05	−0.0000857	Dominated

HITT = heparin-induced thrombocytopenia and thrombosis; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

Subgroup Analysis: Medical Patients Without Stroke

The subgroup analysis for medical patients without stroke is presented in Table 43 and Table 44. In this subgroup, no differences in efficacy (VTE) or harms (bleeding) were found. As such, UFH is the preferred strategy, as the cost of UFH is slightly lower compared with LMWH, but effectiveness and all other cost categories are the same.

Table 43: Reference Case Results — Medical Patients Without Stroke

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
UFH	276.74	-	0.30613	-	-
LMWH	277.98	1.25	0.30613	0	Dominated

ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; UFH = unfractionated heparin.

Table 44: Reference Case Disaggregate Costs ($) — Medical Patients Without Stroke

Strategy	Ten-Day Drug Cost	Bleeding Cost From Prophylaxis	HIT Cost	VTE Cost
UFH	63.61	14.24	169.44	29.45
LMWH	64.86	14.24	169.44	29.45

HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

The HIT scenario was also applied to the subgroup of medical patients without stroke (Table 45). LMWH became the preferred strategy in the HITT scenario reference case and in all sensitivity analyses.

Table 45: HITT Scenario and Sensitivity Analysis — Medical Patients Without Stroke

Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
Reference case UFH	153.49	−0.0000749	Dominated
UFH, 5,000 IU t.i.d. UFH	185.30	−0.0000749	Dominated
OR of HIT (Martel et al.[32]), lower CI, 0.01 UFH	168.96	−0.0000824	Dominated
OR of HIT (Martel et al.[32]), upper CI, 0.82 UFH	29.70	−0.0000150	Dominated
RR of HIT (Junqueira et al.[21]), 0.24 UFH	129.42	−0.0000632	Dominated
RR of HIT (Junqueira et al.[21]), lower CI, 0.07 UFH	158.65	−0.0000774	Dominated

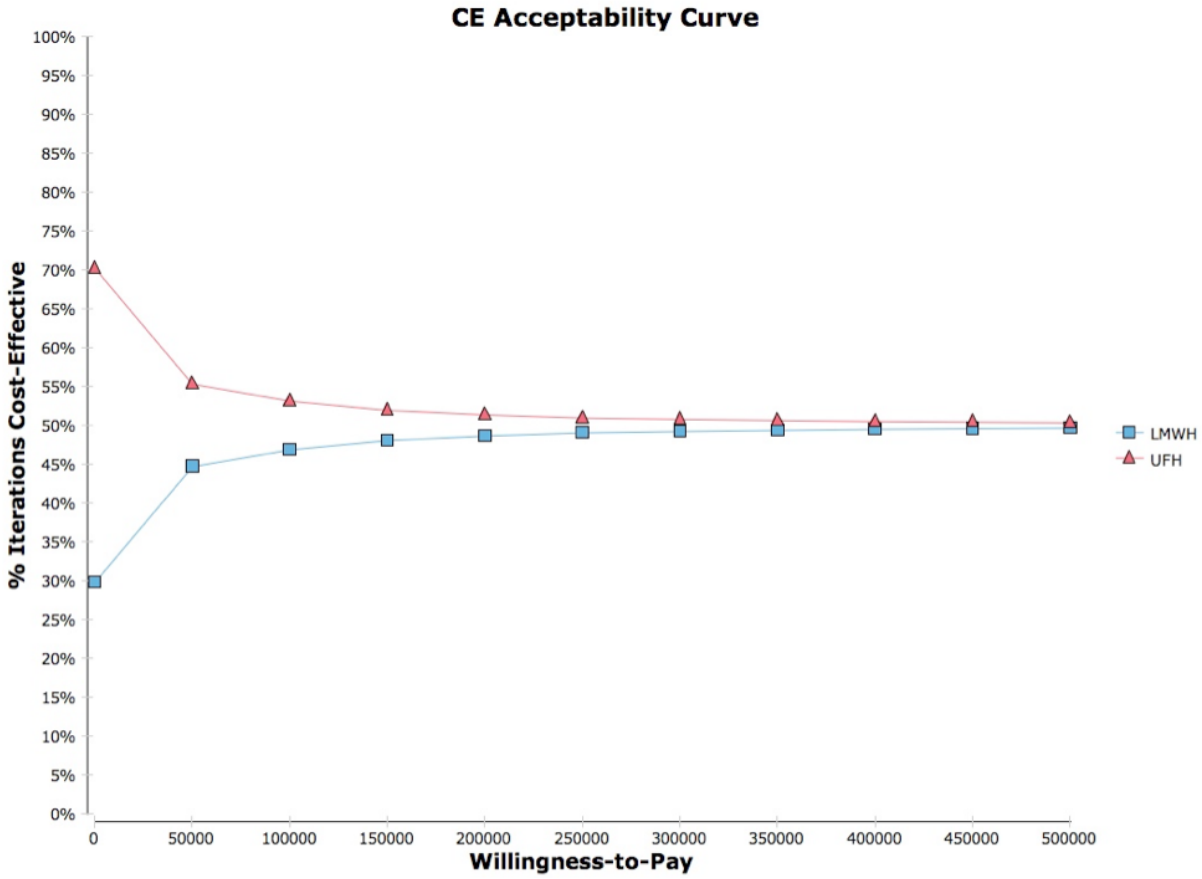
Sensitivity Analysis	Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
RR of HIT (Junqueira et al.[21]), upper CI, 0.82 UFH	29.70	−0.0000150	Dominated
Risk of HIT (suspected), 0.00855 (McGowan et al.[31]) UFH	131.05	−0.0000640	Dominated
Risk of HIT (suspected), 0.00855 vs. 0.0049 (RR, 0.573) UFH	61.51	−0.0000304	Dominated
Risk of HIT (positive), 0.00165 UFH	24.28	−0.0000124	Dominated
Risk of HIT (positive), 0.00165 vs. 0.00061 (RR, 0.37) UFH	16.63	−0.0000087	Dominated
Risk of HIT, lower CI, 0.0002 UFH	1.85	−0.0000015	Dominated
Risk of HIT, upper CI, 0.027 UFH	416.54	−0.0002022	Dominated
Proportion of HITT, 43% vs. 19% (McGowan et al.[31]) UFH	186.00	−0.0000974	Dominated
Proportion of HITT, lower CI, 40% UFH	168.73	−0.0000855	Dominated
Proportion of HITT, upper CI, 54.3% UFH	212.31	−0.0001160	Dominated
HIT cost, $1,489; HITT cost, $10,550 (McGarry et al.[5]) UFH	42.94	−0.0000749	Dominated
DOAC VTE (APX/RIV/DAB) UFH	153.49	−0.0000749	Dominated

APX = apixaban; CI = confidence interval; DAB = dabigatran; DOAC = direct oral anticoagulant; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; ICUR = incremental cost-utility ratio; OR = odds ratio; QALY = quality-adjusted life year; RIV = rivaroxaban; RR = relative risk; UFH = unfractionated heparin; vs. = versus; VTE = venous thromboembolism.

Probabilistic Sensitivity Analysis

Cost-effectiveness acceptability curves for surgical patients (base case and HIT scenario) are shown in Figure 2 and Figure 3. In surgical patients, UFH was the preferred strategy at all willingness-to-pay thresholds evaluated. The probability that UFH is the preferred strategy decreases as the willingness-to-pay threshold increases, approaching 50% as the willingness-to-pay reaches $500,000 per QALY (Figure 2).

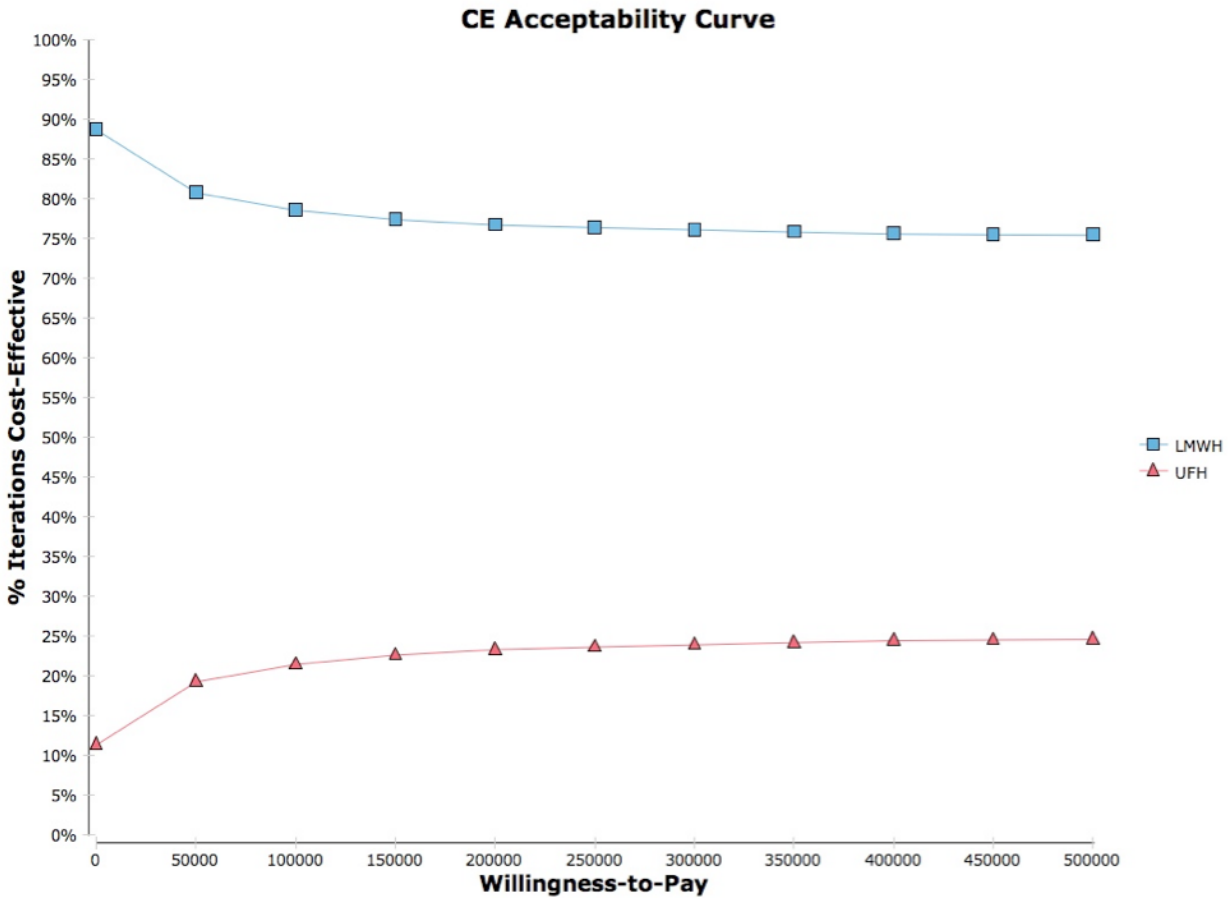
Figure 2: Cost-Effectiveness Acceptability Curve — Surgical Reference Case



CE = cost-effectiveness; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

When the HITT scenario was incorporated into the analysis, LMWH became the preferred strategy at all evaluated willingness-to-pay thresholds (Figure 3).

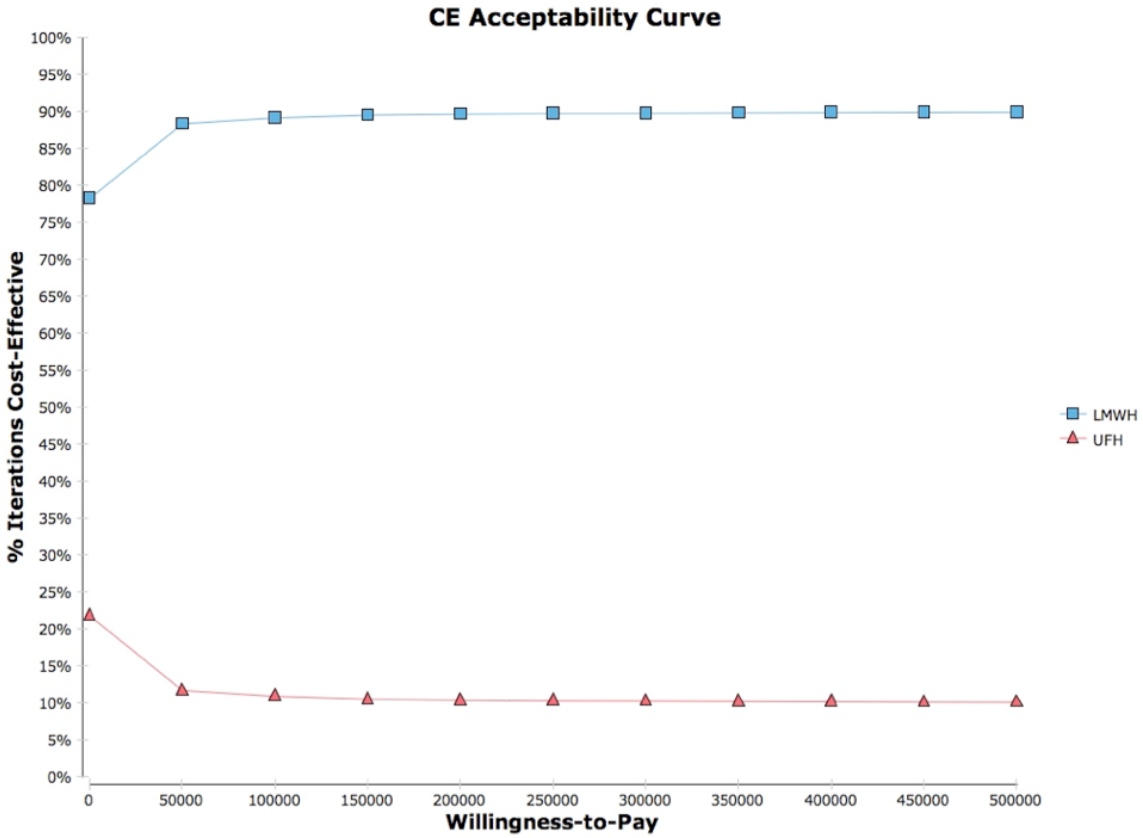
Figure 3: Cost-Effectiveness Acceptability Curve — Surgical HITT Scenario



CE = cost-effectiveness; HITT = heparin-induced thrombocytopenia and thrombosis; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

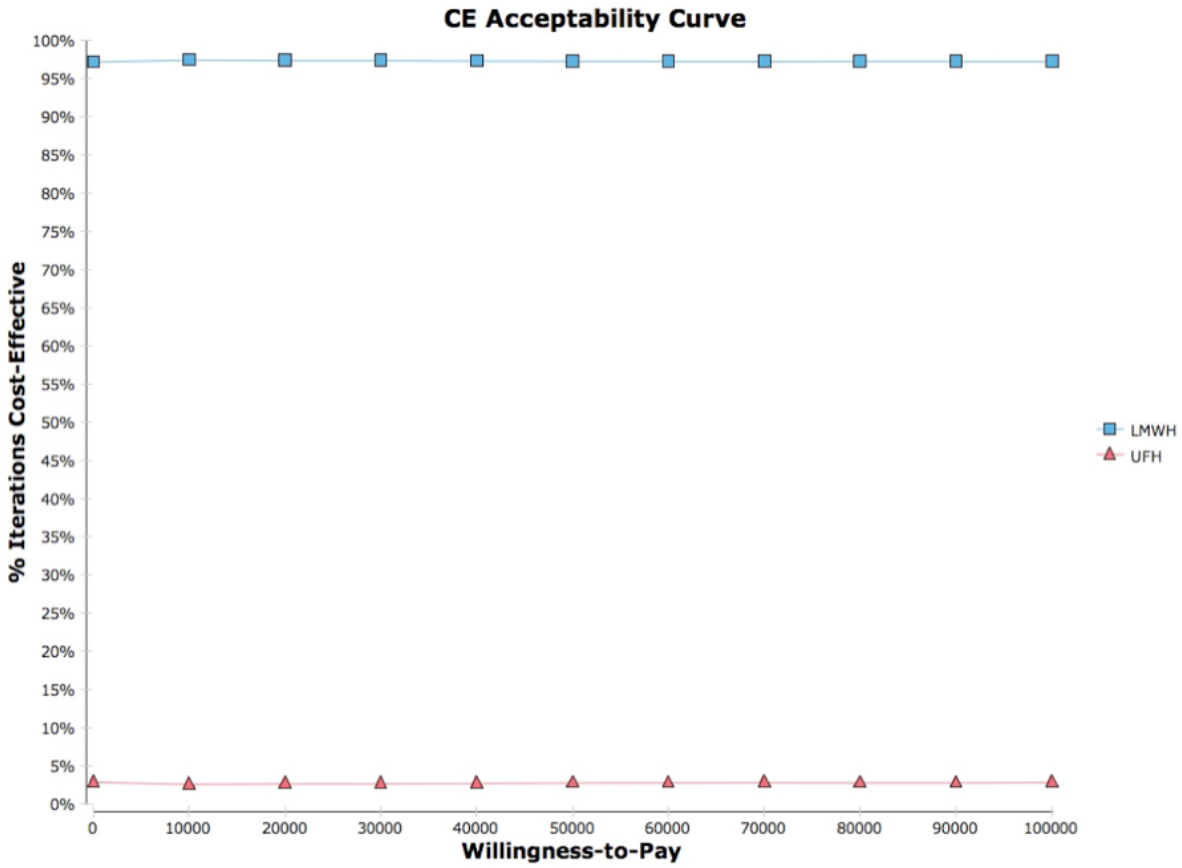
Cost-effectiveness acceptability curves for medical patients (reference case and HITT scenario) are shown in Figure 4 and Figure 5. In both analyses, LMWH was the preferred strategy at all willingness-to-pay thresholds up to $500,000.

Figure 4: Cost-Effectiveness Acceptability Curve — Medical Reference Case



CE = cost-effectiveness; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

Figure 5: Cost-Effectiveness Acceptability Curve — Medical HITT Scenario



CE = cost-effectiveness; HITT = heparin-induced thrombocytopenia and thrombosis; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

Discussion

In this economic analysis comparing two heparin-based treatments for the prevention of VTE in either hospitalized medical or surgical (non-orthopedic/general abdominal) patients, LMWH was associated with lower costs and slightly greater benefits compared with UFH in models where HIT was incorporated (where the risk of HITT was lower with LMWH compared with UFH). This finding was largely unchanged when a wide range of sensitivity and scenario analyses was conducted.

The difference in the occurrence of HIT associated with LMWH versus UFH is an influential variable. While this outcome was deemed to be important, the studies included in the clinical review did not report on this outcome. A priori, only statistically significant results from the clinical review were used and, as such, it was not incorporated in the reference case. However, HITT was deemed to be of key importance and, as such, estimates of HITT, including the report of a lower risk of

HITT with LMWH compared with UFH, were assessed. If LMWH has a reduced risk of HITT compared with UFH, as indicated by available studies, it is the more attractive strategy. Despite the low event rate, the cost of this complication is large and is associated with an increased short-term risk of death. It is likely that the true long-term impact of HITT is underestimated in the economic model, as the short-term and long-term disutility of arterial and venous thrombosis was not modelled due to lack of evidence. As such, the model likely underestimates the attractiveness of LMWH compared with UFH for the prevention of VTE in the hospital setting.

Despite the de novo systematic search and clinical review, there is uncertainty in the relative efficacy and safety of LMWH compared with UFH. Efficacy and safety are discussed in detail in the clinical review; but, briefly, in medical patients, a reduced risk of VTE was observed with no increase in bleeding using LMWH (compared with UFH). The reduced risk of VTE may be driven by the inclusion of studies in patients with stroke; when studies evaluating stroke were excluded, the benefit of LMWH (compared with UFH) for preventing VTE was no longer observed. It should be noted, however, that the incremental costs and benefits attributable to a reduction in VTE observed in the reference case for medical patients is relatively small.

Similarly, the clinical systematic review identified an increased risk of bleeding in surgical patients with LMWH (compared with UFH). Note that the consequences of major and minor bleeding encountered with VTE prevention are different than those observed in patients receiving systemic full-dose anticoagulation (as used in the treatment of VTE). Furthermore, based on definitions of major and minor bleeding where provided in studies, as well as expert opinion, this complication leads to relatively minor clinical consequences. However, the inclusion of an increased risk of any bleeding with LMWH did lead to an increased cost with this strategy. These increased costs were outweighed by averting costs attributable to HITT, when the HITT scenario was included. However, it should be noted that there is uncertainty in the risk of bleeding. The economic model used, a priori, “any” bleed (including both major and minor bleeding) that had an OR of 1.72 (95% CI, 1.15 to 2.56). However, when minor and major bleeding were considered individually, only minor was statistically significant. This may suggest there is no difference in the risk of major bleeding, or that the analysis was underpowered to detect true differences (the event rate for major bleeding is much lower than for minor bleeding).

One impetus for conducting this economic evaluation is the change in acquisition costs of heparin products over time. Using information from the Alberta Health provincial drug formulary, the average daily cost of enoxaparin has decreased from $21.50 in 2005 to $8.65 in 2015 (and is likely lower for hospital formularies). While it is more difficult to obtain cost information on UFH (it is largely provided to hospitalized patients and therefore may not be on many provincial formularies), limited data suggest the average daily cost of UFH used for VTE prevention has

increased from $3.50 per day in 2005, to between $5.30 and as high as $9.37 per day in more recent years. The reduction in costs of LMWH are likely attributable to competition, and although patent protection on various LMWH has expired, no generic products have entered the market; if this occurs, the cost may decrease further. The increasing cost in UFH may be attributable to concerns around the safety of this product, which have led to a more stringent manufacturing process that has subsequently increased production costs.[2]

While the incremental costs of drug acquisition and complications are relatively small on a per-patient basis, these costs are magnified by the large number of hospitalization episodes that occur every year (estimated to be approximately three million in Canada in 2013).[54] As such, even if a fraction of the total annual number of hospitalized patients require VTE prevention, small differences in drug acquisition costs, as well as other consequences (including VTE, bleeding, or HITT), should be carefully considered, even if the per-patient incremental impact is small.

Limitations

This analysis has several limitations that merit consideration. The primary consideration is the limitations informing relative efficacy, as identified in the clinical review. However, unless the results of the clinical review are dramatically different than reality for VTE and bleeding, the conclusions would remain the same when the reduced risk of HITT with LMWH (compared with UFH) is factored in. While HITT was identified as a clinically important outcome in the clinical review, included studies did not report on this outcome. As described in the clinical review, limited data from previous studies (including systematic reviews of both randomized controlled trials and retrospective reviews from a tertiary care centre in Toronto) suggest that use of LMWH in surgical and medical patients is associated with a reduction in the risk of HITT compared with UFH. In most of the sensitivity analyses performed within the HITT scenario analyses in both medical and surgical patients, LMWH remained the dominant strategy over a wide range of relative safety estimates, and the dominance of LMWH was lost only if a very low baseline risk of HITT in surgical patients was considered.

This economic evaluation is also limited by the lack of data on long-term costs and consequences. If major bleeding leads to significant long-term morbidity or mortality, the model may have underestimated the true impact of this in surgical patients, although it should be noted that while “any” bleeding was greater with LMWH, it was not significant for “major” bleeding. Further, the study definitions of major bleeding, as well as expert opinion on the consequences of major bleeding, suggest that if any underestimation occurred, it is likely to be minor. Further, the long-term consequences of HITT, especially that of thrombosis, are not included due to the uncertainty of the true nature of disability incurred and the very rare occurrence of serious long-term disability, in the

opinion of clinical experts. While the magnitude of this is likely to be small, as indicated earlier, this may underestimate the benefit of LMWH compared with UFH if the estimates of a reduced risk of HITT with LMWH hold true.

The incremental QALYs between treatment strategies were very small when differences were noted. This is driven by the relative infrequency of many of the events and the short time period over which they likely impact quality of life. In circumstances where a comparator is more costly and more effective, the ICUR can become “unstable” or very large due to costs being divided by a very small number. When interpreting results, it is useful to consider the individual incremental costs and benefit when evaluating the incremental cost-effectiveness ratio.

Finally, there is variability in the costs of these drugs, which are opaque. This is contributed to by confidentiality agreements that occur between manufacturers and RHA and hospital purchasing departments. To address this, ratio analyses were conducted to allow RHAs and individual hospitals to determine the scenario that reflects the incremental costs of these two drugs observed in their respective context.

Conclusion

This economic analysis suggests that LMWH is the preferred strategy to prevent venous thromboembolic events in hospitalized medical and surgical patients. Current trends, of increasing UFH drug acquisition costs and decreasing costs for LMWH products, are likely to make the LMWH-based VTE prevention strategy appear even more attractive with time, if these trends continue. However, there is uncertainty in this analysis, which is in large part driven by the assumption that use of LMWH results in a lower risk of HITT and its attendant consequences. If future studies demonstrate that these differences are absent or are smaller than assumed here, the results of this analysis should be revisited.

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