

**TITLE: Low Molecular Weight Heparins versus Unfractionated Heparin for Thromboprophylaxis: A Review of the Cost-Effectiveness**

**DATE:** 01 September 2009

**CONTEXT AND POLICY ISSUES:**

Low molecular weight heparins (LMWH) have emerged as an important alternative to unfractionated heparin (UH) for both prophylaxis and treatment of venous thromboembolism (VTE) in acutely ill medical patients.<sup>1</sup> Clinical studies<sup>2-5</sup> show that LMWH given once or twice a day is as effective and safe as UH, and may be superior to UH. LMWH have a clinical advantage over UH in terms of low risk of major bleeding, recurrence of VTE, and low mortality rates.<sup>3,5-7</sup> However, drug acquisition cost per day for LMWH is about three times the acquisition costs for UH [C\$12.08/day for LMWH versus C\$4.14/day for UH (values in 2007)].<sup>8</sup> Since UH is inexpensive relative to LMWH in terms of drug acquisition cost, the adoption of LMWH necessitates demonstration of economic attractiveness over UH, taking into account other costs associated with clinical outcomes occurring throughout the continuum of care. The present study provides a review of economic studies comparing LMWH with UH for prevention of VTE in patients receiving thromboprophylaxis following major orthopedic surgery.

**RESEARCH QUESTION:**

What is the cost-effectiveness of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis following major orthopedic surgery?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and August 2009. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, and economic studies.

***Disclaimer:*** The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

***Copyright:*** This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

***Links:*** This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

**SUMMARY OF FINDINGS:****Patients receiving VTE prophylaxis following major orthopedic surgery**

The literature search did not identify economic evaluation studies assessing the cost-effectiveness of LMWH versus UH for thromboprophylaxis following major orthopedic surgery. Clinical outcomes of thromboprophylaxis [rates of VTE, major bleeding, and heparin-induced thrombocytopenia (HIT)] occur across different medical inpatient populations;<sup>9,10</sup> hence, the results of economic evaluation studies comparing LMWH and UH for prevention of VTE in general medical inpatients may be applied to patients receiving VTE prophylaxis following major orthopedic surgery and other medical inpatient populations. Therefore, economic evaluation studies comparing LMWH and UH for the prevention of VTE in general medical inpatients were included in the review.

**Economic evaluation studies in general medical inpatients**

A total of nine economic evaluation studies<sup>1,2,4,8,11-15</sup> were included in the review. Of the nine studies, one was conducted in Canada,<sup>8</sup> six in USA,<sup>1,2,4,11,12,15</sup> one in the UK,<sup>14</sup> and one in Germany.<sup>13</sup> Two studies<sup>11,15</sup> are designed as cost-utility analyses (i.e. results expressed in terms of incremental cost per quality adjusted life years, QALYs). Five studies<sup>1,2,8,13,14</sup> are cost-effectiveness analyses (results expressed in terms of immediate and/or intermediate clinical outcomes such as incremental cost per DVT averted, major bleeding avoided, death avoided etc.), and two studies<sup>4,12</sup> are cost analyses (examine costs only). For each study, patient characteristics, study perspective, model structure, major findings, and results of sensitivity analysis are reviewed.

*Cost-utility studies*

Leykum *et al.* (2006)<sup>15</sup> used a decision analytic model to examine the cost-utility of UH compared with the LMWH enoxaparin for VTE prevention for “all medical inpatients for whom VTE prophylaxis was appropriate.” Costs were analyzed from the perspectives of a healthcare payer and healthcare system in the US.

Estimates of effectiveness included development of VTE, bleeding complications, HIT, progression to heparin-induced thrombocytopenia with thrombosis (HITT), and mortality rate. Equal efficacy on rate of VTE was adopted from Kleber *et al.*, 2003 and assumed to be equal between UH and enoxaparin. The authors assumed equal rates of bleeding and other drug adverse events between interventions based on the results of a study by Samama *et al.*, 1999. Rate of HIT and HITT for UH was derived by Leykum *et al.* from pooling four studies (McLeod *et al.*, 2001, Warkentin *et al.*, 1995, 2000, and 2003) while similar rates for enoxaparin were derived from pooling three studies (Girolami *et al.*, 2003, Nand *et al.*, 1995, and Lewis *et al.*, 2001) identified in the MEDLINE data base. Mortality rate secondary to thrombosis in treated patients were adopted from a study by Lewis *et al.*, 2001, and health state utility values were adopted from “Cost Effectiveness Analysis Registry at the Harvard Center of Risk analysis.”

In the first scenario, representing the perspective of healthcare payer, costs due to medications (enoxaparin, UH, argatroban, and Coumadin), laboratory tests, physician visits and consultations, and additional healthcare resource utilization resulting from development of HIT and caring for patients of HITT were included. Physician charges and additional resources utilized due to development of HIT and caring for HITT were derived from a 2004 Medicare

reimbursement. Medication costs obtained from the pharmacies of urban and suburban acute facilities were used in the analysis. In the second scenario (from the perspective of healthcare system of USA) potential loss of income from additional days of hospitalization for HIT and HITT was included. This entailed the inclusion of opportunity cost of additional hospitalization day.

In the model, patients receiving either UH or enoxaparin may experience HIT with possibility of either thrombocytopenia being resolved or developing HITT. Once HITT is developed it can resolve or cause death. Patients experiencing HIT accumulate the associated cost and additional costs if they develop HITT.

The results showed that compared to UH, enoxaparin yielded an incremental daily cost of US\$28.61 and incremental QALY of 0.00629, resulting to incremental savings ratio of US\$4,550.17/QALY from the perspective of healthcare payer. Results of sensitivity analysis did not change cost-effectiveness position of enoxaparin. Incidence of HIT and rate of thrombosis among patients with HIT were the most influential inputs on savings per QALY. The superiority of enoxaparin was attributed to its tendency to reduce development of HIT and HITT. From the perspective of healthcare system, the result showed that inclusion of potential loss of income to the healthcare system did not make enoxaparin more economically attractive (enoxaparin and UH produced daily costs of US\$91.59 and US\$72.33, respectively). UH was associated with less daily costs compared to enoxaparin when medication price for UH was decreased and when length of hospitalization for patients with HIT or HITT was increased.

The validity of key assumption by Leykum *et al.*<sup>15</sup> that enoxaparin and UH were equal in terms of efficacy in preventing VTE and adverse events, particularly major bleeding cannot be confirmed; and therefore, weakens the strength of the evidence. The majority of cost-effectiveness analyses reviewed herein<sup>1,2,8,11-13</sup> demonstrated differences in efficacy between enoxaparin and UH. Also, as noted by the author, death and recovery were the only clinical outcomes considered, therefore, QALYs produced by interventions may have been underestimated since other clinically important outcomes such as amputation and or other loss of function were not considered.

Heerey and Suri (2005)<sup>11</sup> used a Markov modeling approach to conducted a cost-effectiveness analysis comparing the LMWH dalteparin at a high dose of 5000U, dalteparin 2500U, and UH for preventing venous thromboembolism (VTE) in mixed-sex patient cohort undergoing elective abdominal surgery. The analysis was performed from the perspective of healthcare system in the US. The results were presented in terms of cost per incremental cost-effectiveness ratio (ICER) per QALY gained.

The model consisted of three arms of patient cohorts with each cohort receiving either dalteparin 5000U or dalteparin 2500U once daily, or UH (5000U twice a day) in the preoperative period of prevention of VTE. Patients in each arm were assumed to start taking their respective drug 2 hours prior to surgery and continue for a total of 10 days. Clinical efficacy was expressed in terms of drug complications segmented into three groups: immediate, early, and late. Immediate complications were defined as those complications occurring during the initial 30 days of "index hospitalization" (DVT, PE, major bleeding, and death). Patients who had VTE during the immediate period were routinely prescribed oral warfarin to treat VTE. Early complications are those occurring during the initial 1 to 6 months following surgery. Late complications were defined as complications occurring after the first 6 months following surgery and related to immediate complications (recurrent VTE and mild or severe post-phlebotic syndrome).

Risk estimates (probability of VTE, drug related bleeding complications, and death due to VTE), incidence of major bleeding during index hospitalization as the results of VTE prophylaxis, and death rate due to VTE during the initial 30 days of follow-up were estimated by pooling five published clinical trials (identified by Heerey and Suri by searching MEDLINE) that compared either different doses of dalteparin or compared dalteparin with UH for post-surgical prevention of VTE. Data from previous published meta-analyses by Gould *et al.* (1999) and White *et al.* (1999) were used by Heerey and Suri for the incidence of major bleeding following UH treatment for VTE and for major bleeding during oral warfarin treatment, respectively. Health state utility of 0.93 (with a range of 0.79 – 1) for severe post-phlebotic syndrome was adopted from a study by Lenert and Soetikno (1997) while a health state utility ranging from 0.81 to 0.84 for healthy women and men were calculated from a study by Fryback *et al.* (1993).

Costs modeled are those associated with medications (with per unit cost derived from average wholesale price), management of immediate complications (DVT, PE, major bleeding, and death), warfarin acquisition, patient assessment, and outpatient follow-up for patients with VTE.

The results showed that dalteparin 5000U was associated with the highest average lifetime total cost (US\$46,308), followed by dalteparin 2500U (US\$45,882); UH was associated with the lowest average lifetime total cost (US\$45,855). Dalteparin 5000U yielded an incremental effectiveness gain of 0.0179 QALYs over dalteparin 2500U and 0.0208 QALYs over UH; hence producing an ICER of US\$23,799/QALYs over dalteparin 2500U and an ICER of US\$21,779/QALYs over UH. Dalteparin 2500U yielded an incremental effectiveness of 0.0029 QALYs over UH, giving an ICER of US\$9,310/QALYs.

The results of one-way sensitivity analysis under different scenarios showed that dalteparin maintained an ICER of less than US\$50,000/QALY except when the probability of death in the first year was increased by 25%. The result of Monte Carlo simulation (50,000 simulations of patient cycles) aimed at examining the probability distribution of ICER results showed that at an ICER threshold of US\$50,000/QALY, dalteparin 5000U compared to UH and dalteparin 2500U had a 50% chance of being cost-effective.

The validity of the findings by Heerey and Suri 2005<sup>11</sup> are questioned on the following grounds: (i) similar estimates for long-term complications in patients with VTE in the first 30 days for each arm were applied which may have contributed to minimal differences observed in effectiveness and costs among interventions; (ii) calculation of health state utilities used in the model lack transparency. Patients undergoing abdominal surgery are expected to have reduced health-related quality of life prior to experiencing complications related to VTE prophylaxis. It is not known how (if at all) Heerey and Suri 2005<sup>11</sup> factored in reduced health state utility due to underlying condition; and (iii) characteristics and quality of the five clinical studies pooled to derive the estimates for the model is not known.

## Cost-effectiveness studies

Lynd *et al.* (2007)<sup>8</sup> conducted a probabilistic cost-effectiveness analysis of enoxaparin versus unfractionated heparin (UH) for the prophylaxis of deep-vein thrombosis (DVT) in patients with moderate or severe trauma (injury severity score of  $\geq 9$ ). Life-time horizon was used to estimate the ICER in terms of DVT averted and life year gained (LYG) from the perspective of the Canadian healthcare payer.

In the model, the patient faces a probability of developing DVT and when diagnosed and confirmed to have DVT (i.e. true positive results by ultrasound), the patient undergoes treatment

with the possibility of major bleed with chance of death. Patients with probability of developing DVT but falsely diagnosed as negative face the probability of developing pulmonary embolism (PE) with chance of dying before PE is clinically detected, confirmed, and treated.

Clinical efficacy of either intervention included intermediate endpoint (DVT averted) and final endpoints (prevention of PE and deaths secondary to either PE or DVT prophylaxis or treatment-related major bleeds). Efficacy data were obtained from randomized controlled trials (RCT) identified by Lynd *et al.* through an electronic search in Medline and EMBASE databases. RCTs evaluating enoxaparin or UH (either head to head, or to any other prophylactic agent) in patients with major trauma which reported data efficacy (prevention of DVT) and safety (i.e. major bleeding) were used for data extraction.

Costs associated with diagnosis, prophylaxis, and treatment were modeled. Costs included the cost due to drug acquisition per day, ultrasound, intensive care unit (ICU) stay, hospital stay, spiral computed tomography, and two views by portable x-ray. Data on drug acquisition cost were obtained from St Joseph's Healthcare in Hamilton, ON, Canada whereas cost of administration and procurement were derived from expert opinion and were uniformly applied across interventions. Length of stay in ICU and general ward stratified by whether or not patients experienced a DVT were obtained from Canadian Institute for Health Information.

The results showed that that enoxaparin was more effective in terms of DVT averted (yielding an incremental effectiveness of 0.085 DVTs averted) and produced an incremental cost of C\$90. Relative to UH, enoxaparin yielded an ICER of C\$1,059 per DVT averted (C\$ values in 2003). When the results were expressed in terms of LYG, enoxaparin was C\$90 more costly and produced 0.13 less LYG than UH, suggesting that UH is the dominant strategy. When willingness-to-pay threshold per DVT averted was set to C\$20,000 there was a 93% chance that enoxaparin was cost-effective. When the same threshold was applied in terms of LYG there was a 91% chance that UH was cost-effective. The authors noted that relative to the UH arm, enoxaparin arm was associated with higher rates of major bleeds, which resulted in higher mortality rates and fewer LYG.

While the study by Lynd *et al.*<sup>8</sup> contributes to the overall evidence regarding cost-effectiveness of LMWH, the quality of data on clinical efficacy was not reported and may have affected the validity of the results. Data on major bleeding during prophylaxis with both enoxaparin and UH was extracted from a study conducted in 1996 by Geerts *et al.* The same study was used for data on proximal DVT in both the UH and enoxaparin groups. The authors neither provided detail regarding the quality of the source nor stated the reason as to why a meta-analysis was not possible. Moreover, as per selection criteria, RCTs comparing either UH or enoxaparin with any other prophylaxis agent were used as data source; suggesting that superiority of either intervention may not necessarily reflect its relativity to its comparator.

Wade and Spruill (2008)<sup>2</sup> conducted a cost-analysis of dalteparin administered once daily compared to UH administered 3 times a day in patients undergoing surgical intervention for gynaecologic malignancy. The analysis was performed in the US from "an institutional perspective in 1000 patients over a 5-day period." Model parameters were derived from published literature identified by searching the PubMed database. Studies reporting types and number of patients, type and duration of prophylaxis, incidences of total DVT, proximal DVT, non-fatal PE, and major bleeding episodes were included. Data from selected studies were pooled and averaged when more than one study was selected examining a specific prophylaxis drug.



Clinical efficacy measures of prophylaxis were expressed in terms of development of DVT, major bleeding, and development of nonfatal PE. The authors identified 11 studies examining either UH or dalteparin as DVT prophylaxis following surgery for gynaecologic malignancy but only three met selection criteria (Fricker *et al.*, 1988; Clarke-Pearson *et al.*, 1993 and Maxwell *et al.*, 2000). Table 1 shows the results of the selected studies as reported by Wade and Spruill 2008.<sup>2</sup>

**Table 1: Clinical Results of studies used by Wade and Spruill 2008<sup>2</sup> to derive clinical inputs**

Study & number of patients	DVT episodes	Nonfatal PE	Major bleeding
Fricker <i>et al.</i> , 1988 (UH = 32 pts, dalteparin = 28 pts)	UH = 0 Dalteparin = 0	UH = 2 Dalteparin = 0	UH = 1 Dalteparin = 2
Clarke-Pearson <i>et al.</i> , 1993 (UH = 107 pts, IPC = 101 pts)	UH = 3 IPC = 1	UH = 0 IPC = 0	UH = 3 IPC = 0
Maxwell <i>et al.</i> , 2000 (total 121 pts reported, number in each group not reported)	UH = 2 IPC = 1	UH = 0 IPC = 0	UH = 4 IPC = 0

DVT = deep vein thrombosis; IPC = intermittent pneumatic calf compression; PE = pulmonary embolism; pts = patients; UH = unfractionated heparin

From the above three trials, Wade and Spruill<sup>2</sup> derived the following incidence rates for dalteparin: 1.9% proximal DVT, 0% nonfatal PE, and 5.6% major bleeding. Incidence rates for UH were estimated as 2.7% proximal DVT, 1.8% nonfatal PE, and 3.5% major bleeding. Costs included in the calculation of total cost for each prophylaxis including costs associated with purchasing prophylaxis drug, and costs of diagnosing and managing DVT and nonfatal PE.

Incremental cost was calculated by dividing all costs associated with prophylaxis regimens by the difference in thromboembolic episodes averted with each prophylaxis regimen. Therefore, the outcome of cost analysis represent total savings (in 2007 US\$ values) per thromboembolic event averted assuming one specific regimen was used as DVT prophylaxis. UH and dalteparin was associated with a savings of US\$5400 and US\$7800 per death avoided, respectively. The result of incremental analysis showed that if routinely used, dalteparin 5000 units daily would save US\$6961.60 for each thromboembolic episode averted over UH 5000 units every 8 hours. The results of sensitivity analysis showed that UH yielded a savings of US\$5142.89 over dalteparin when lower range estimates of DVT and major bleedings are considered. Applying upper range estimates for DVT and major bleeding led to US\$7630.20 savings by dalteparin over UH.

A weakness of the Wade and Spruill<sup>2</sup> study is a lack of transparency in methodology used. Methods used to calculate key clinical parameters (proximal DVT, nonfatal PE, and major bleeding) from selected clinical studies cannot be verified. Also, the sensitivity analyses do not indicate the key parameters that may have a large influence in total savings per DVT avoided. For example, the question remains regarding the impact of higher rates of major bleeding observed in dalteparin arm on its savings over UH. Moreover, dalteparin loses its superiority when avoidance of death from DVT, PE, and major bleeding is considered as final endpoint for the regimes. UH led to an avoidance of death at a lower cost than dalteparin (US\$5400 versus US\$7899). The authors did not explain why this is the case.

Schadlich *et al.* (2006)<sup>13</sup> used a decision-analytic model to examine cost-effectiveness of enoxaparin 40 mg once a day relative to no pharmacological prophylaxis (NPP) and relative to

unfractionated heparin (UH) 500IU three times daily. Each intervention was used in addition to elastic bandage stocking and physiotherapy in the prevention of VTE in immobilized acutely ill medical patients without impaired renal function or extreme body weight. The analysis was performed from the perspective of hospitals in Germany, with a time horizon of 8 days of thromboprophylaxis plus up to 31 days of treatment of major intracranial bleed.

Clinical efficacy of interventions was defined as incidence of VTE (DVT, PE, or both) and incidence of episodes of major bleeding; hence the results of the analysis were expressed in terms of incremental cost per VTE and major bleeding avoided per 1,000 patients. Data on efficacy were adopted by Schadlich *et al.* from two RCTs (Samama *et al.*, 1999 and Kleber *et al.*, 2003) and a meta-analysis by published by Mismetti P, *et al.*, 2000. Other required inputs such as transition probabilities, frequency of coagulation control during prevention and treatment of VTE, and diagnostic accuracy for DVT or PE were obtained from pharmaco-economic and medical publications identified by a literature search in the MEDLINE database.

Cost parameters of the model included costs associated with drug acquisition, respective diagnostic procedures for DVT and PE, treatment of major bleeding during VTE treatment, and treatment of secondary pneumonia after PE. Wholesale prices were used to estimate drug acquisition costs, materials, and disposables for laboratory examinations. Estimates of other cost parameters were derived from a survey involving medical clinics and hospital pharmacies in Germany.

Point estimates of the respective model input values were exclusively applied in the base case analysis. The results showed that total cost per 1,000 patients was €72,570 and €43,715 for enoxaparin and NPP, respectively. Enoxaparin and NPP yielded 13.42 and 39.49 clinically detected and treated VTEs per 1,000 patients, respectively. This translated to 26.07 VTEs avoided by enoxaparin and a savings of €17,380 in costs for diagnostics and treatment for VTEs, related episodes of major bleeding, and treatment of secondary pneumonia after PE. Compared to NPP, enoxaparin produced an ICER of €1106 per clinically avoided VTE [ $(€72,570 - €43,715)/26.07 = €1106$ ].

Total hospital cost per 1,000 patients in the UH arm was €128,395 versus €72,570 for patients in the enoxaparin arm. UH and enoxaparin led to 12.13 and 4.46 episodes of major bleeding, respectively. This translated to €55,825 cost saving with enoxaparin and 7.67 episodes of major bleeding avoided by enoxaparin. Results of incremental cost-effectiveness analysis showed that enoxaparin dominated UH (i.e. enoxaparin is more effective in avoiding major bleeding and less costly).

The results of sensitivity analysis showed that when enoxaparin is compared with NPP, the incidence rate of proximal DVT with NPP was the most influential model input on ICER followed by probability of true positive symptoms of proximal DVT, incidence rate of distal DVT with NPP, and incidence of major bleeding. When enoxaparin was compared with UH, cost per minute of nursing time was the most influential model parameter on cost savings with enoxaparin followed by incidence rate of major bleeding with UH, incidence of major bleeding with enoxaparin, and drug acquisition cost of enoxaparin.

The results of the probabilistic model showed the incremental cost of enoxaparin ranging between €-500 and €9255 per VTE avoided compared to NPP. The results of the Monte Carlo simulation showed that for 95% of the 10,000 simulations, the ICER per VTE avoided of enoxaparin relative to NPP ranged between €86 (2.5% percentile) and €2973 (97.5%)

percentile). Enoxaparin remained dominant over UH in >95% of simulations. For 95% of the 10,000 simulations, cost savings with enoxaparin per 1,000 patients ranged between €996 (2.5% percentile) and €130,131 (97.5% percentile). For 95% of the simulations, episodes of major bleeding avoided by enoxaparin per 1,000 patients ranged between 4.33 (2.5% percentile) and 11.07 (97.5% percentile).

The study provided a contribution to the evidence on cost-effectiveness of LMWH relative to UH. Their model is transparent and reproducible. However, their analysis specifically targeted hospitals in Germany; therefore, results of this study are not generalizable to the Canadian healthcare setting. The authors stated that 84% of the savings with enoxaparin compared to UH is due to saving in nursing time, mainly attributed to lower frequency of administering enoxaparin. According to the authors, nursing time in Germany hospitals accounted for 66% of total cost to the hospital in 2001. Therefore, the reported cost savings with enoxaparin may not be applicable in Canada and elsewhere where drug acquisition cost or costs due to management of major bleeding may account for the largest share of the total cost.

Offord *et al.* (2004)<sup>14</sup> used a model published by Lloyd *et al.* (2001) to examine the cost-effectiveness of enoxaparin (40 mg/day) compared with UH (5000IU twice/day) or no prophylaxis in immobilized patients with acute heart failure (or acute respiratory failure or who had an acute episode of an inflammatory bowel or rheumatic disease in association with pre-defined risk factors for VTE) from the perspective of the UK National Health Service.

The study was carried out at an acute teaching hospital (St. Thomas's hospital) based in central London. The authors reviewed medical admissions that took place from January 2000 to December 2000 using predefined criteria to determine the numbers of patients admitted to St. Thomas hospital fulfilling the exact inclusion criteria of a previously published clinical study by Samama *et al.*, 1999 that compared enoxaparin and placebo. The Samama *et al.* study enrolled immobilized patients with acute heart failure, acute respiratory failure, or patients with an acute episode of an inflammatory bowel or rheumatic disease in association with pre-defined risk factors for VTE).

The model adopted results of the clinical study by Samama *et al.* and the meta-analysis conducted by Mismetti P *et al.*, 2000 examining the efficacy of UH and LMWH in prevention of VTE in medical patients. Clinical efficacy was defined as number of VTE events (DVT, PE, or both) and major bleeding. Costs included in the analysis were costs due to drug acquisition, confirmation of DVT, managing confirmed DVT, managing confirmed PE, and major bleeding. Cost estimates were adopted from an economic evaluation of enoxaparin conducted by Nuijten *et al.*, 2003 in Spain.

The results showed that UH 5000IU twice a day was associated with highest cost of thromboprophylaxis (£199,000 per 2000 patients) followed by enoxaparin (£198,000 per 2000 patients), and no prophylaxis (£176,000 per 2000 patients). Compared with no prophylaxis, enoxaparin produced a cost-effectiveness ratio of £796 per VTE event avoided and £185 per life year saved. Sensitivity analysis on key inputs (drug acquisition costs and diagnostic costs applicable to St Thomas' hospital) did not change the results (i.e. UH remained the highest cost strategy) but resulted in the enoxaparin strategy being less costly than the no prophylaxis strategy (£134,000 versus £165,000 per 2000 patients).

McGarry *et al.*, 2004<sup>1</sup> compared the cost-effectiveness of prophylaxis with a LMWH with that of prophylaxis with UH for the prevention of VTE in acutely ill medical inpatients in the US. A hypothetical cohort of 10,000 patients with various serious medical conditions was assumed to



receive one of three thromboprophylaxis strategies: (i) enoxaparin 40 mg daily; (ii) UH 5000 UI (UI not defined in the article) twice a day or; (iii) no prophylaxis. For each arm, the study estimated costs of prophylaxis and treatment within a 30-day period, mortality, 30-day risks of VTE (including DVT and/or PE), and complication of prophylaxis and treatment (HIT and bleeding).

In the model, patients receiving either type of prophylaxis face the probability of experiencing HIT (either symptomatic or asymptomatic) and bleeding (major or minor), with a possibility of death from major bleeds and symptomatic HIT. Patients experiencing neither HIT nor bleed are at risk of developing DVT and therefore undergoing clinical diagnosis and positive results is followed by confirmatory duplex ultrasound and treatment once DVT is confirmed. Patients receiving DVT treatment face a probability of HIT and bleeds. Patients receiving DVT treatment without experiencing HIT and bleeds face probability of developing PE and subsequently chance of death shortly after the acute event or survive and be clinically diagnosed and confirmed by ventilation-perfusion scan or computed tomography, and undergo PE treatment once confirmed positive. Patients can die from treated PE or untreated PE or other underlying medical conditions.

Clinical efficacy was defined as drug-related adverse events (particularly HIT and bleed), DVT, and PE. Risk of failure and occurrence of adverse events for each prophylaxis were obtained from published literature while the risks of DVT with LMWH-treated patients and untreated patients were obtained from the placebo-controlled trial published in 1999 by Samama *et al.* The risk of prophylaxis failure in the UH arm was estimated from the results of a meta-analysis (conducted by Mismetti P, *et al.*, 2000) of studies comparing LMWH to UH in medical patients.

The study was conducted from the perspective of a third-party health insurer, therefore only direct costs were considered. Costs associated with drug acquisition and laboratory supplies and procedures, physician visits (both inpatient and outpatient), and hospital inpatient days were included in the analysis.

The results of the study showed that the risk of DVT, PE, and attributable deaths were lowest among patients receiving thromboprophylaxis and highest among those receiving no prophylaxis. In a cohort of 10,000 acutely ill patients, compared to no thromboprophylaxis, the use of enoxaparin was associated with prevention of 860 cases of DVT, 171 cases of PE, and 44 deaths attributed to both DVT and PE, whereas 776 cases of DVT, 155 cases of PE, and 28 attributable deaths would be prevented by using UH. Expected costs of prevention, diagnosis, and management of DVT for enoxaparin, UH, and no prophylaxis were about US\$3.5 million, US\$3.7 million, and US\$3.1 million, respectively (US\$ values in 2001). The results of the incremental analysis showed that relative to no prophylaxis, enoxaparin was cost-effective, producing an ICER of US\$9,100 per death averted. Enoxaparin dominated UH (i.e. enoxaparin was more effective in preventing deaths and less costly).

Three sub-analyses were performed: for patients with heart failure, for patients with respiratory disease, and for patients with infectious disease. The results of the incremental analysis showed that for each sub-analysis, enoxaparin dominated UH. One-way sensitivity analyses were performed. Changes in underlying risk of death and risk of DVT did not alter the dominance of enoxaparin over UH. To lose its dominance, enoxaparin drug acquisition cost would have to increase by more than 50%.

Probabilities and costs used in the model were estimated by gathering and combining data from various studies of unknown methodologies and qualities. The validity of the estimates and

unknown precision of the process involved question the validity and generalizability of the findings of McGarry *et al.*<sup>1</sup>

The authors explained that “to estimate the risk of prophylaxis failure among patients receiving UH we used the results of a recent meta-analysis of trials that compared LMWH to UH in medical patients and applied the summary risk-ratio of 0.83 to the risk of prophylaxis failure in the LMWH arm of the MEDENOX trial” (trial by Samma *et al.*, 1999). The authors assumed that the risk of DVT in the UH arm was a constant multiple of the risk of DVT in the enoxaparin arm irrespective of the underlying risk of DVT or underlying patient prognosis. The assumption may have impacted the calculations of effectiveness and cost which could have potentially introduced bias into the results against UH. Also, as noted by the authors of the trial by Samma *et al.*, the meta-analysis by Mismetti *et al.*, 2000 used to derive risk estimates excluded some patient populations such as expectant mothers, patients with recent stroke, and patients requiring chronic anticoagulation. Therefore, the findings cannot be extrapolated to these populations.

### *Cost analysis studies*

Dietelzweig *et al.*, (2008)<sup>12</sup> used a decision analytic model to compare average costs for UH, enoxaparin, and no prophylaxis in medical patients at risk from the perspective of “commercial and medical audiences” in the US. The time horizon for the model was two years and the outcome of the model was expressed in terms of two-year total average cost per patient.

A hypothetical patient cohort emulating hospitalized acutely ill general patients (average age 73 years) at risk of VTE was divided into three arms (10,000 patients each) with each arm receiving either enoxaparin 40 mg daily for 5 days, UH 5,000IU twice a day for 5 days, or no prophylaxis. The first 90 days following hospital admission the model measured primary VTE (DVT or PE) and drug-related outcomes and in the remaining 640 days VTE complications and recurrent VTE events were modeled.

Clinical outcomes measured were DVT, PE, minor and major bleed, symptomatic and asymptomatic HIT, and death. All clinical inputs including probabilities applied in the model for the first 90 days following hospital admission were adopted from previously published cost-effectiveness study by McGarry *et al.*, 2004<sup>1</sup> reviewed herein. Input parameters applied after 90 days were extracted from various studies.

Costs due to acquiring the prophylactic drug, treatment of adverse events (bleed, hospital stay, symptomatic and asymptomatic HIT), diagnosis, VTE treatment, and treatment of complications were modeled. Drug acquisition costs were obtained from the Red Book of May 2006 and some data on treatment of adverse events were adopted from Zhao *et al.*, 2006 while some were adopted from Medical Payment Schedule 2005. Diagnosis costs were derived from Medical Physician Fee Schedule 2005 and costs due to VTE treatment were adopted from a study by Spyropoulos 2007 while cost of treating complications were derived from MacDougal *et al.*, 2006 and Medical Physician Fee Schedule 2005.

In the model, patients could experience a primary VTE in the first 90 days. Patients with and without primary VTE at day 90 were moved into post-primary VTE phase to be monitored for recurrence of VTE and death. Once immediately transferred to the post-primary VTE phase only patients with primary VTE in the first 90 days were allowed to transition between states beyond the 90-day period. Patients experiencing adverse events during the first 90 days were assumed treated or died; therefore, exited the model. In the post-primary VTE phase, patients entered a

Markov process comprising six health states (no prior VTE, post-primary DVT, post-primary PE, post-DVT recurrence, post-PE recurrence, and death) with a monthly cycle.

Base case results showed that the percentage of VTE events per 10,000 patients was 6.8%, 7.9%, and 17.9% in the enoxaparin arm, in the UH arm, and in the no prophylaxis arm, respectively, with relative risk of VTE estimated at 13.6% lower with enoxaparin than with UH, and 16.8% lower with enoxaparin than no prophylaxis. Respective projected incidence rate of DVT and PE was 5.5% and 1.4% for enoxaparin compared to 6.3% and 1.6% for UH. Compared to UH, the respective risk of major bleed and symptomatic HIT was 44% and 85.2% lower with enoxaparin.

Average total costs per patient were US\$1,264 for enoxaparin, US\$1,585 for UH, and US\$2,245 for no prophylaxis. About 70% of the costs for enoxaparin and UH were incurred in the first month of hospital admission, while about 50% of the costs of the no prophylaxis arm were incurred after one month of admission. Treatment of VTE accounted for the largest share of total cost for each arm. The results of threshold analysis showed that enoxaparin and UH yielded similar number of deaths when the rate of primary VTE for enoxaparin increased by 23.5% or when the rate of primary VTE for UH decreased by 21.2%. The results of Monte Carlo simulation indicated that among scenarios examined, no scenario resulted in higher costs for enoxaparin than the cost for UH or no prophylaxis strategy.

Limitations of Dietelzweig *et al.*'s study<sup>12</sup> include the assumption that patients received prophylaxis for five days whereas reported standard length of prophylaxis is between 6 days and 14 days.<sup>6</sup> As noted by Dietelzweig *et al.*,<sup>12</sup> shorter prophylaxis length may have resulted in higher incidence of VTE than would be observed in clinical trials. Also, the model assumed that rate of VTE recurrence following enoxaparin, UH, and no prophylaxis was similar across all strategies, which cannot be verified.

Shorr *et al.*, (2007)<sup>4</sup> used decision analytic model to investigate costs of LMWH compared with UH for prevention of DVT in 1,000 hypothetical acutely ill medical patients from the perspective of third-party payer in the US.

In each arm, the authors observed four possible mutually exclusive clinical outcomes: development of DVT, drug-related major bleeding, evolution of HIT, or "an eventful hospitalization." Rates of DVT and major bleeding for each arm (LMWH and UH) were obtained by Shorr *et al.* from the meta-analysis published by Mismetti *et al.*, 2000 (meta-analysis of prospective RCTs comparing LMWH with UF in medical patients). Shorr *et al.* (2007)<sup>4</sup> pooled two prospective observational studies (Girolami *et al.*, 2003 and Harbrecht *et al.*, 2004) to determine the incidence of HIT in medical population.

In addition to drug acquisition costs, other costs included in the analysis were those due to management and treatment of DVT, bleeding, and HIT. The author reviewed cost-analysis studies to assess the costs associated with clinical events. Cost of DVT was extrapolated by Shorr *et al.* from a study by De Lissoyoy and Subedi (2002) and estimates of costs associated with major bleeding and HIT were adopted from McGarry *et al.* (2004). A direct pharmacy acquisition cost for LMWH and UH obtained from a major, non-federal academic medical centre in Washington, DC were adopted in the model. Calculation of drug acquisition cost per patient for DVT prevention with UH was based on twice a day dosing and for LMWH was calculated based on 40 mg of enoxaparin per day for 5 days.

Base case results showed that 20 cases of DVT, 10 patients with major bleeding complication, and 14 cases of HIT were observed among 1,000 hypothetical patients in the UH arm. Respective DVT cases, patients with major bleeding episodes, and HIT cases in the LMWH (enoxaparin) arm was 17, 5, and 1. Prevention of DVT with UH was associated with a higher cost than enoxaparin (US\$405,534 compared to US\$315,929). Among 1,000 patients, routine use of enoxaparin instead of UH produced US\$89,465 savings. Results of sensitivity analysis depicted by a tornado diagram showed that baseline HIT rate was the most influential input on savings per patient with LMWH followed by odds ratio of LMWH DVT, cost of HIT, and baseline rate of DVT. Costs of DVT, bleed, and UH drug acquisition had little impact on savings per patient.

A major limitation of Shorr *et al.*<sup>4</sup> is poor and non-transparent methods of quantifying costs. The authors adapted previously published total costs associated with clinical outcomes of interest. The assumptions underlying the calculations of cost due to DVT, major bleed, and HIT are not known as they were adopted from previous studies. Shorr *et al.*<sup>4</sup> noted, for example, that costs due to HIT accounted for 35% of the total cost in the UH arm, yet the authors gave no detail on quantification of HIT costs despite its large influence on the total cost for the UH arm. Also, the authors used a drug acquisition cost from a medical centre on the grounds that wholesale prices “had been shown to inflate pharmacy costs and do not take into account price discounts given to major purchase.” A proper conduct of economic evaluation calls for an economic model that is generalizable; the use of drug price charged to a specific medical center limits generalization of the results the study.

## LIMITATIONS

No economic evaluation studies comparing LMWH with UH for prevention of VTE following major orthopedic surgery were identified. The results of the eight non-Canadian economic studies<sup>1,2,4,11-15</sup> examining various patient populations suggests that LMWH is cost-effective compared to UH although the drug acquisition cost for LMWH is higher than that for UH. Overall, studies suggest that cost-effectiveness of LMWH is mainly attributed to lower incidence of HIT and PE, fewer episodes of major bleeding, and low mortality rate compared to UH. Clinical advantages of LMWH over UH offset its higher drug acquisition cost, hence reducing accumulative costs associated with treatment and prevention of DVT.

However, the results should be interpreted with caution. The studies were conducted across different countries and perspectives; therefore, data and results cannot be compared directly across studies because factors affecting cost-effectiveness such as study perspective, labour costs, and drug acquisition costs vary among countries. Similarly, clinical data adopted from different countries may not be generalizable to the Canadian setting.

In addition, the reviewed studies employed different methods and assumptions with unknown precision and validity. For example, Leykum *et al.*<sup>15</sup> assumed that enoxaparin and UH were equal in terms of efficacy in preventing VTE and adverse events, particularly major bleeding. The assumption negates the finding that LMWH is attributed to lower incidence rate of major bleeding.<sup>3,5-7</sup> Also, different costing methods employed across studies limits the applicability of the study results to other settings because the methods specifically reflect the perspective of the study and respective healthcare system of the country. For example, the study conducted in Germany by Schadlich *et al.*<sup>13</sup> found that 84% of savings with enoxaparin compared to UH was due to saving in nursing time. According to the authors, nursing time in Germany hospitals accounted for 66% of the total cost to the hospital; which may not be the case for hospitals in Canada.



There is uncertainty around the validity of the findings because an appropriate analytical time horizon for examining cost-effectiveness of thromboprophylaxis is not known. Time horizon used varied markedly across studies. One study examined costs and efficacy of thromboprophylaxis for 5 days<sup>2</sup> and one study for 10 days,<sup>11</sup> whereas some studies examined costs and effects over a period of 2 years<sup>12</sup> or a life-time.<sup>8,15</sup>

The results of the Canadian study (Lynd *et al.*, 2007<sup>8</sup>) suggested that UH dominates LMWH in terms incremental cost per LYG due to a higher incidence of major bleeds in patients receiving LMWH. LMWH was cost-effective compared to UH when an intermediate outcome measure (DVT averted) was considered. Clinical data used in the Canadian study<sup>8</sup> was adopted from a study published in 1996 by Geerts *et al.*, in which more major bleeds were observed in patients receiving enoxaparin than in patient receiving UH. The finding of Geerts *et al.* negates the results of the most referenced RCT (Samama *et al.* 1999) and meta-analysis (Mismetti P, *et al.*, 2000). The results of the Canadian study<sup>8</sup> could change in favor of LMWH if recent clinical data demonstrating fewer major bleed episodes with LMWH were used.

### CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

No economic evaluation studies comparing LMWH with UH for prevention of VTE following major orthopedic surgery were identified. The results of the included economic evaluation studies support the cost-effectiveness of LMWH compared to UH in various medical inpatient populations, which may also be relevant to the orthopedic surgery patient population. The results of the reviewed studies are limited by variations in costing methods, quality and validity of clinical inputs used, analytical time horizon, study perspective, and assumptions, which are potential considerations for decision-making. It may not be appropriate to compare the results across the studies, and this report reviewed the cost-effectiveness of either LMWH or UH as demonstrated in the various studies.

### PREPARED BY:

Stephen K. Membe, MDE, Health Economist  
Emmanuel Nkansah, BEng, MLS, MA, Information Specialist  
**Health Technology Inquiry Service**  
Email: [htis@cadth.ca](mailto:htis@cadth.ca)  
Tel: 1-866-898-8439

## REFERENCES:

1. McGarry LJ, Thompson D, Weinstein MC, Goldhaber SZ. Cost effectiveness of thromboprophylaxis with a low-molecular-weight heparin versus unfractionated heparin in acutely ill medical inpatients. *Am J Manag Care* 2004;10(9):632-42. Available: [http://www.ajmc.com/media/pdf/AJMC04sep\\_McGarry632\\_642.pdf](http://www.ajmc.com/media/pdf/AJMC04sep_McGarry632_642.pdf) (accessed 2009 Aug 11).
2. Wade WE, Spruill WJ. Cost-effectiveness of dalteparin versus unfractionated heparin as venous thromboembolism prophylaxis in malignant gynecologic surgery. *Am J Ther* 2008;15(6):512-5.
3. Gómez-Outes A, Rocha E, Martínez-González J, Kakkar VV. Cost effectiveness of bemiparin sodium versus unfractionated heparin and oral anticoagulants in the acute and long-term treatment of deep vein thrombosis. *Pharmacoeconomics* 2006;24(1):81-92.
4. Shorr AF, Jackson WL, Weiss BM, Moores LK. Low-molecular weight heparin for deep vein thrombosis prophylaxis in hospitalized medical patients: results from a cost-effectiveness analysis. *Blood Coagul Fibrinolysis* 2007;18(4):309-16.
5. Nutescu EA. Easing the economic burden of acute coronary syndromes: cost-effectiveness of emerging therapies. *Am J Manag Care* 2006;12(16 Suppl):S444-S450. Available: [http://www.ajmc.com/media/pdf/A164\\_06decNutescuS444to50\\_.pdf](http://www.ajmc.com/media/pdf/A164_06decNutescuS444to50_.pdf) (accessed 2009 Aug 11).
6. Pineo GF, Hull RD. Economic and Practical Aspects of Thromboprophylaxis With Unfractionated and Low-Molecular-Weight Heparins in Hospitalized Medical Patients. *Clin Appl Thromb Hemost* 2009.
7. Jones TE, Smith BJ, Polasek JF. Pharmacoeconomics of low-molecular-weight heparins: limitations of studies comparing them to unfractionated heparin. *Expert Opin Pharmacother* 2004;5(9):1887-97.
8. Lynd LD, Goeree R, Crowther MA, O'Brien BJ. A probabilistic cost-effectiveness analysis of enoxaparin versus unfractionated heparin for the prophylaxis of deep-vein thrombosis following major trauma. *Can J Clin Pharmacol* 2007;14(2):e215-e226. Available: [http://www.cjcp.ca/pdf/CJCP\\_e215\\_F.pdf](http://www.cjcp.ca/pdf/CJCP_e215_F.pdf) (accessed 2009 Aug 11).
9. Raskob GE. Low molecular weight heparin for venous thromboembolic disease. In: *UpToDate* [Online database]. Version 17.2. Waltham (MA): UpToDate; 2008 (accessed 2009 Aug 27).
10. Pineo GF. Prevention of venous thromboembolic disease. In: *UpToDate* [Online database]. Version 17.2. Waltham (MA): UpToDate; 2009 (accessed 2009 Aug 27).
11. Heerey A, Suri S. Cost effectiveness of dalteparin for preventing venous thromboembolism in abdominal surgery. *Pharmacoeconomics* 2005;23(9):927-44.

12. Deitelzweig SB, Becker R, Lin J, Benner J. Comparison of the two-year outcomes and costs of prophylaxis in medical patients at risk of venous thromboembolism. *Thromb Haemost* 2008;100(5):810-20.
13. Schädlich PK, Kentsch M, Weber M, Kammerer W, Brecht JG, Nadipelli V, et al. Cost effectiveness of enoxaparin as prophylaxis against venous thromboembolic complications in acutely ill medical inpatients: modelling study from the hospital perspective in Germany. *Pharmacoeconomics* 2006;24(6):571-91.
14. Offord R, Lloyd AC, Anderson P, Bearne A. Economic evaluation of enoxaparin for the prevention of venous thromboembolism in acutely ill medical patients. *Pharm World Sci* 2004;26(4):214-20.
15. Leykum L, Pugh J, Diuguid D, Papadopoulos K. Cost utility of substituting enoxaparin for unfractionated heparin for prophylaxis of venous thrombosis in the hospitalized medical patient. *J Hosp Med* 2006;1(3):168-76.