TITLE: Low Molecular Weight Heparins Versus Unfractionated Heparin for Thromboprophylaxis in Surgery, Cancer and General Medicine: A Review of the Cost-effectiveness and Safety

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CONTEXT AND POLICY ISSUES

Low molecular weight heparins (LMWH) have emerged as an important alternative to unfractionated heparin (UFH) for both prophylaxis and treatment of venous thromboembolism (VTE) in acutely ill medical patients.[1] Both LMWH and UFH are recommended for VTE prophylaxis in hospitalized medical patients.[2] LMWHs available in Canadian market include enoxaparin, tinzaparin, dalteparin and nadroparin.[3] Clinical studies[4-7] show that LMWH given once or twice a day is as effective and safe as UFH, and may be superior to UFH. LMWHs have a clinical advantage over UFH in terms of a lower risk of major bleeding, lower recurrence of VTE, and lower mortality rates.[5,7-9] However, drug acquisition costs per day for LMWH is about three times the acquisition costs for UFH [C$12.08/day for LMWH versus C$4.14/day for UFH (values in 2007)].[10,11] Since UFH is inexpensive relative to LMWH in terms of drug acquisition cost, the adoption of LMWH necessitates demonstration of economic attractiveness over UFH, taking into account other costs associated with clinical outcomes occurring throughout the continuum of care. LMWH are at least as effective antithrombotic drugs as UFH, however, it is still unclear whether the safety profiles of LMWH and UFH differ.[12] The important adverse events of heparin includes heparin-induced thrombocytopenia (HIT), an adverse drug reaction presenting as a prothrombotic disorder related to antibody-mediated platelet activation,[13] and bleeding. In 2009, CADTH published a review on the cost-effectiveness of LMWH compared with UFH. [11] It was reported in that review that LMWH appeared more cost-effective compared to UFH in various medical inpatient populations. This review is intended to provide an updated overview of cost-effectiveness evidence comparing LMWH with UFH for prevention of VTE in patients receiving thromboprophylaxis following surgery, patients with cancer and general medical patients as well as an overview of the comparative safety profile in terms of the incidence of HIT and bleeding.

RESEARCH QUESTIONS

1. What is the cost-effectiveness of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis for patients for surgery, cancer and general medicine?

2. What is the safety of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis for patients following surgery, cancer and general medicine?

KEY FINDINGS

The evidence from Canadian settings supports the cost-effectiveness of LMWH compared to UFH in medical patients. In terms of HIT or bleeding risk, LMWH was superior to UFH in patients following surgery, but similar or superior to UFH in general medical patients. The results of the findings should be interpreted with caution due to the limitations of methodological quality and various heterogeneities in dosing regimens, time horizon, study perspective and assumptions.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and economic evaluations. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2009 and Jun 3, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients undergoing surgery Patients with cancer Patients in general medicine
Intervention	Low molecular weight heparins (i.e. enoxaparin, tinzaparin, dalteparin and nadroparin)
Comparator	Unfractionated heparins
Outcomes	Cost-effectiveness, Safety: Heparin induced thrombocytopenia, bleeding (major and minor bleed)
Study Designs	Economic evaluations Health Technology Assessment report/ Systematic review/Meta-analysis

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1, presented duplicate data of an included study, or the study was on a LMWH not marketed in Canada.

Critical Appraisal of Individual Studies

The methodological quality of the included systematic reviews (SR) or meta-analyses (MA)were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[14] Economic evaluations were assessed using the 35-item Drummond's checklist.[15,16] A numeric score was not calculated for each study, instead the strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 978 citations. Upon screening titles and abstracts, 52 potentially relevant articles were retrieved for full-text review. Of the 52 potentially relevant articles, 34 reports were included in this review. Eighteen[17-34] evaluated the cost-effectiveness of LMWH compared with UFH. Sixteen[2,12,13,35-47] reviewed the comparative safety profile (HIT or bleeding risk) of LMWH versus UFH. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

What is the cost-effectiveness of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis for patients for surgery, cancer and general medicine?

Of the eighteen included economic analysis, four analyses[28-30,48] were conducted in patients after surgery, including two[29,48] conducted in USA. The remaining 14 studies were on general medicine patients. Four studies[18,24,26,32] were conducted in Canadian settings and two[21,25] were based on a multiple-nation setting including Canada in patients with acute ischemic stroke (AIS),[21,25] ST-elevation myocardial Infarction (STEMI),[32] and other general medical patients.[18,24,26]

A summary of the characteristics of all included studies can be found in Appendix 2. The characteristics of the economic analysis conducted in Canadian settings are briefly summarized below:

Thirugnanam et al.[18] conducted a systematic review on economic analyses of VTE prevention strategies in hospitalized patients. Twelve economic evaluations based on randomized controlled trials (RCTs) were included.

Pineo et al. performed two systematic reviews to determine the economic impact of enoxaparin versus UFH for VTE prophylaxis after AIS from a hospital perspective,[21] and from a payer's perspective,[25] respectively. A decision-analytic model was constructed and hospital-based costs were analyzed using clinical information from the PREVAIL trial.[49] Total hospital costs were calculated based on mean costs in the Premier database and from wholesaler's acquisition data. From the payer's perspective, drug costs and Medicare & Medicaid Services event costs were used.

In a time-and-motion study, Pettigrew et al.[24] tested the hypothesis that tinzaparin may reduce nursing time and total health care costs compared with UFH. Data on health care resource use associated with anticoagulation during hemodialysis for chronic renal failure were collected at an academic hospital in Quebec. Nursing time was recorded for 8 nurses performing 16 dialysis sessions for 4 patients receiving tinzaparin and 4 receiving UFH (2 dialysis sessions per patient). Nurses had ≥ 1 year of experience supervising hemodialysis. Annual costs of nursing time and health care resources were estimated. Estimated annual nursing times per patient were 0.8 vs. 11.5 hours in the first year and 0.6 vs. 10.2 hours in subsequent years for tinzaparin vs. UFH, respectively.

Wilbur et al.[26] conducted a pharmacoeconomic analysis comparing LMWH with UFH heparin for prophylaxis of VTE in medicine patients. A decision-analytic model assessed costs and outcomes of LMWH compared to UFH for thromboprophylaxis in at-risk hospitalized general medicine patients from an institutional perspective. The outcome of interest was the incremental cost-effectiveness ratio (ICER) for preventing deep vein thrombosis (DVT) and combined untoward events (pulmonary embolism [PE], major bleed, and death). The time horizon of the model was the hospital stay.

Welsh et al.[32] evaluated the cost-effectiveness of enoxaparin compared with UFH in STEMI patients undergoing pharmacological reperfusion based on the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment - Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 trial.[50] A model was created to analyze the cost-effectiveness of enoxaparin compared with UFH among STEMI patients treated with fibrinolysis within Canada. Clinical outcomes were derived from published results of the main trial. Resource use costs were first assessed based on United States Diagnosis-Related Group values for hospitalizations and Current Procedural Terminology codes for outpatient visits and tests. Both were then converted using Canadian local costs. Survival and life expectancy were estimated from Framingham survival data. The ICER was expressed as cost per life year gained.

What is the safety of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis for patients following surgery, cancer and general medicine?

Sixteen systematic reviews[2,12,13,35-47] were identified to assess the comparative safety profile of LMWHs compared with UFH for thromboprophylaxis. Four studies[13,36,37,39] reviewed the comparative risk of bleeding or HIT between LMWH and UFH used in surgical patients. The remaining studies were in general medical patients including patients with AIS, STEMI and undergoing hemodialysis due to end stage renal disease (ESRD) or hospitalized patients. Four systematic reviews were conducted in USA; two in Canada, two in France, two in Italy; one in UK, one in Netherland, one in China, one in Brazil, one in Israel and one in Lebanon. Most systematic reviews[2,12,35,37-40,42-47] included RCTs only. Three systematic reviews[13,36,41] included both RCTs and non-RCTs. Sample size ranged from two[13] to 27[12] studies. Fourteen[2,12,35,36,38-47] reported bleeding as the outcome of AEs; one reported HIT[13] and one[37] reported both bleeding and HIT.

Summary of Critical Appraisal

What is the cost-effectiveness of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis for patients for surgery, cancer and general medicine?

The strengths and limitations of included economic analyses are summarized in Appendix 4. Overall, the methodological quality of the economic evaluation reports was considered to be low to

moderate. The main methodological limitations were some outcomes were pooled from a small number of studies; time horizons either were too short or varied widely; the perspectives varied; there was significant population heterogeneity of included studies with some analyses; some clinical data was based on the radiologic not clinical VTE detection, which may cause of overestimate of the VTE. Assumptions were not clearly reported in some analyses. (See Appendix 4)

What is the safety of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis for patients following surgery, cancer and general medicine?

The majority of the included SR and MA reports met most AMSTAR criteria and were considered high quality. The main strengths included that research questions were well defined; the literature searches were comprehensive; and study selection and data extraction were independently performed by two reviewers. Some studies[12,35,38,42,44,46] did not assess the publication bias; and some did not provide a list the excluded studies.[2,12,13,35-38,40-42,47] (See Appendix 5)

Summary of Findings

What is the cost-effectiveness of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis for patients for surgery, cancer and general medicine?

In patients following surgery

No economic analyses on surgical patients conducted in Canadian setting were identified. Two economic analyses[23,29] conducted in USA were identified on patients following cancer surgery reported that UFH is more cost-effective strategy than LMWH to prevent postoperative VTE following cancer surgery. (See Appendix 6)

In patients with cancer

No additional economic evidence was identified except the studies reported under the section of patients following cancer surgery above.

In general medical patients

Thirugnanam et al.[18] conducted a systematic review of economic analyses of VTE prevention strategies including LMWH versus UFH in hospitalized patients. Twelve included studies compared LMWH with UFH. It was found that LMWH was most economically attractive among most medical and surgical patients. The authors concluded that LMWH is more economically attractive for VTE prevention in hospitalized patients compared with UFH.

Pineo et al.[21] performed an economic analysis to determine the economic impact from a hospital perspective of enoxaparin versus UFH for VTE prophylaxis after AIS based on the PREVAIL trial.[49] Default drug cost were based on the 2008 US wholesalers' acquisition cost data. It was found that the average cost per patient due to VTE or bleeding events was lower with enoxaparin versus UFH ($422 vs. $662, respectively; net savings $240). The average anticoagulant cost was lower with UFH versus enoxaparin ($259 vs. $360, respectively; net savings $101). However, when both clinical events and drug-acquisition costs were considered, the total hospital cost was lower with enoxaparin compared with UFH ($782 vs. $922, respectively; savings $140). The authors concluded that the higher drug cost of enoxaparin was offset by the reduction in clinical events as

compared to the use of UFH for VTE prophylaxis after AIS, particularly in patients with severe stroke. Pineo et al.[25] also examined the economic impact of enoxaparin after AIS based on the PREVAIL trial[49] from payer's perspective. When considering the total cost of events and drugs, enoxaparin was associated with cost-savings of $895 per patient compared with UFH ($2018 vs. $2913). It was concluded that from a payer perspective, enoxaparin was cost-effective compared with UFH in patients with AIS. The difference was driven by the lower clinical event rates with enoxaparin. Use of enoxaparin may help to reduce the clinical and economic burden of VTE.

Based on a time-and-motion study, Pettigrew et al.[24] examined the hypothesis that tinzaparin may reduce nursing time and total health care costs compared with UFH. It was reported that annual drug costs per patient were CAD $898.56 for tinzaparin and $546.75 for UFH. Estimated total annual costs were CAD $1061.03 vs. $1012.71 in the first year and CAD $917.75 vs. $895.23 in subsequent years for tinzaparin vs. UFH, respectively. Use of tinzaparin was cost saving relative to UFH if tinzaparin price was reduced 30%. Most of the price differential between tinzaparin and UFH is offset by substantial time savings to nephrology nurses.

In the pharmacoeconomic analysis by Wilbur et al.,[26] the cost-effectiveness of LMWH versus UFH for prophylaxis of VTE in hospitalized internal medicine patients was assessed. All costs were determined in 2009 Canadian dollars. In the base-case analysis, LMWH thromboprophylaxis resulted in higher costs ($7.40), but 3.6 and 1.1 fewer DVT and untoward events per 1000 patients, respectively, with associated ICERs of $2042 and $6832. LMWH had the most favorable economic profile in patients with a history of DVT. In the probabilistic sensitivity analysis, in 33% of simulations LMWH were less costly and more effective, whereas the reverse was true for UFH only in 13% of simulations. The authors concluded that LMWH administration is a cost-effective alternative for thromboprophylaxis strategy in Canadian hospitalized medicine patients.

Welsh et al.[32] evaluated the cost-effectiveness of enoxaparin compared with UFH in STEMI patients undergoing pharmacological reperfusion based on the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment - Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 trial.[50] The primary composite end point favored the enoxaparin group over the UFH group (death or recurrent myocardial infarction rate 9.9% versus 12.0%, P<0.001), and was associated with a modest increased cost of $169.50 ($8,757.00 versus $8,587.50, respectively. All costs in Canadian dollars). Life years gained as a result of treatment with enoxaparin was increased by 0.11 years (P<0.05). Enoxaparin was found to be cost-effective, as indicated by an ICER of $4,930 with a 99% probability of costing less than $20,000. The authors concluded that although associated with modest increased direct medication costs, enoxaparin following fibrinolysis improved the clinical efficacy in STEMI patients and increased the life years gained.

What is the safety of low molecular weight heparins versus unfractionated heparin for thromboprophylaxis for patients following surgery, cancer and general medicine?

<u>In patients following surgery</u>

Four studies[13,36,37,39] reviewed the comparative risk of bleeding or HIT between LMWH and UFH used in surgical patients. Statistically significantly fewer bleeding events were reported in LMWH treated patients compared with UFH (Odds ratio [OR]: 0.57, 95% confidence interval [CI]: 0.37 to 0.88)[37]. Statistically significantly fewer HIT were also observed in LMWH treated patients compared with UFH[13,37] ([OR: 0.12, 95% CI: 0.03 to 0.43][37], and [relative risk (RR): 0.24, 95% CI: 0.07 to 0.82][13]).

In patients with cancer

No evidence was identified in this population.

In general medical patients

A. In general medical patients: Four studies[2,42,46,47] reported the comparative risk of bleeding of LMWH versus UFH in general medical patients. Three studies[2,42,47] reported no statistically significant difference in bleeding between LMWH and UFH. One study[46] reported a statistically significant difference in favor of LMWH (RR 0.28, 95%CI: 0.10 to 0.78).

B. In patients with STEMI: Inconsistent results were reported in this group of patients. In two systematic reviews,[40,43] no statistically significant difference in the risk of major bleeding between LMWH and UFH was reported in patients with STEMI. On the other hand, three studies[35,38,41] reported that statistically significantly fewer major bleeding events were observed in LMWH compared with UFH during percutaneous coronary interventions (PCI). The relative risk ranged from 0.63 (95% CI: 0.48 to 0.82) to 0.80 (95%CI: 0.68 to 0.95).

C. In patients with VTE: Three studies[12,44,45] reported major bleeding risk in patients during the treatment of VTE. The results were not consistently reported. One[44] reported a statistically smaller risk of major bleeding with LMWH compared to UFH (OR: 0.58, 95% CI 0.40 to 0.83, P=0.003). The other two did not find a significant difference between LMWH and UFH.[12,45]

Limitations

The evidence of cost-effectiveness analysis of thromoboprophylaxis with LMWH versus UFH after surgery was limited to post-surgical cancer patients in a non-Canadian setting. No economic evaluation studies following major orthopedic surgery were identified. No cost-effectiveness evidence was identified in non-surgical cancer patients. The results of the four Canadian economic studies[18,24,26,32] and two analyses based on multi-nation settings, including Canada,[21,25] in patients with general medical disease examining various patient populations suggested that LMWH is cost-effective compared to UFH although the drug acquisition cost for LMWH is higher than that for UFH. However, the results should be interpreted with caution due to the overall low to moderate methodological quality of the analyses, including heterogeneity in populations, use of various LMWH agents (i.e. LMWH as a drug class or single LMWH agent such as enoxaparin or tinzaparin) or drug dose variation (i.e. low dose or standard dose), and different dosing regimen (fixed or adjusted dose), frequency of administration (twice daily or three times daily), small sample size, short or varied time horizon and different perspectives.

The methodological quality of overall evidence for comparative safety was good. Similar to the economic evidence, the limitations remain in in terms of heterogenous population, sample size and varying dosing regimens.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited cost-effectiveness results from the American setting indicated UFH is more cost-effective than LMWH to prevent postoperative VTE following cancer surgery. The results of the included economic evaluation studies in Canadian settings support the cost-effectiveness of LMWH compared to UFH in patients with VTE, STEMI, and other medical inpatients. This finding is consistent with previous CADTH review published in 2009.[11] In terms of HIT or bleeding risk,

LMWH was found to be superior to UFH in patients following surgery, but similar or superior to UFH in medical patients. The results of the reviewed economic analysis should be interpreted with caution due to the limitations of low to moderate methodological quality and variations in costing methods, quality and validity of clinical inputs used, analytical time horizon, study perspective, and assumptions.

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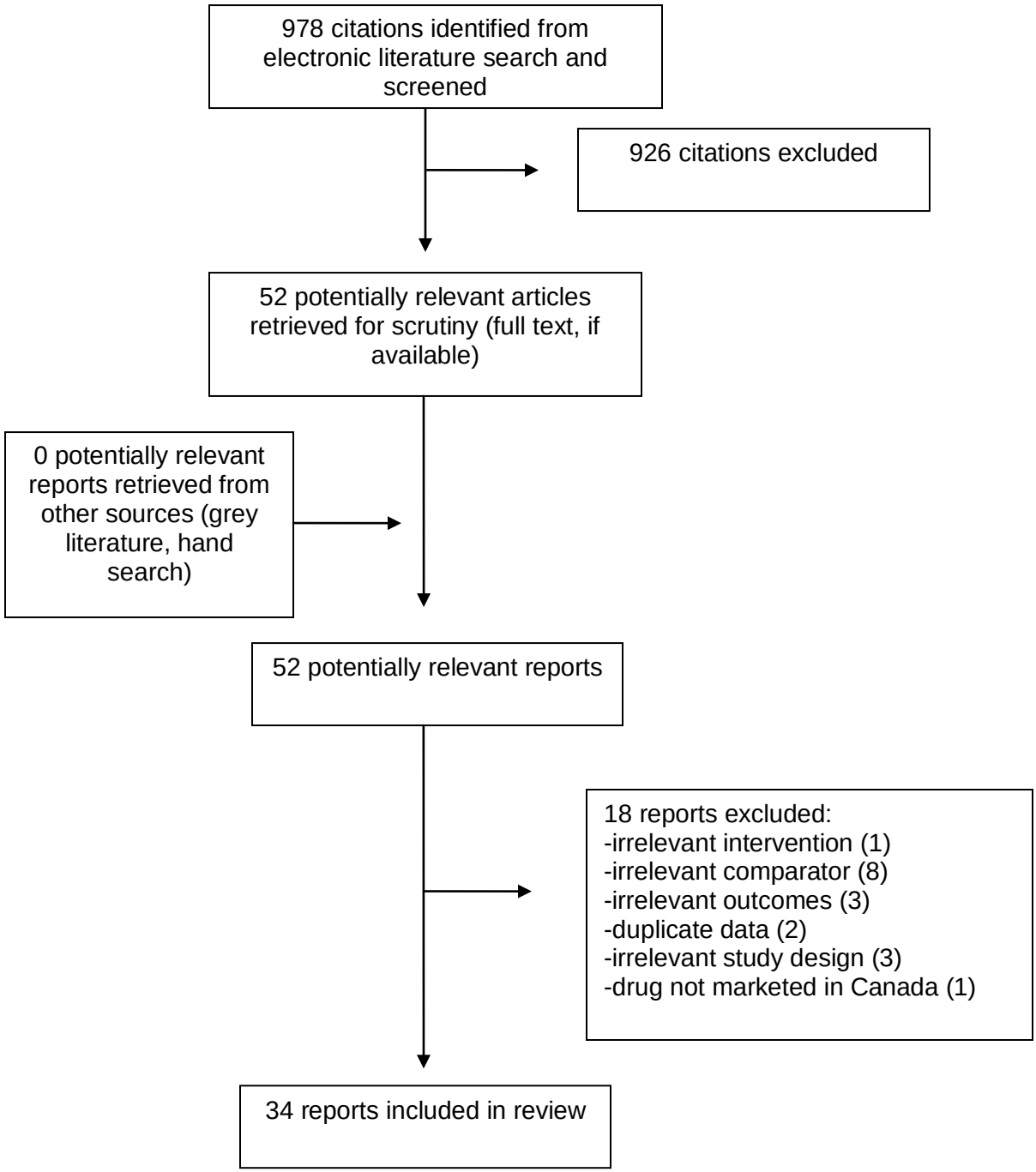
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Study Design, Time horizon	Patient Characteristics	Intervention/ Comparators	Assumptions
Studies conducted in Canadian settings				
Thirugnanam,[18] 2012, Canada	●SR of EA, 12 studies ●TH: 5 days to 8 weeks	TP in hospitalized pts.	ENO/UFH	NR
Pineo,[21] 2012, Canada, USA, Belgium	●Hospital-based costs analyzed ●using clinical data from PREVAIL.[49] TH: 90 days	TP in pts. with AIS,	ENO/UFH	●The simulation adopted a gamma distribution assumption for input sampling for cost
Pettigrew,[24] 2011, Canada	●Time-and-motion study TH: 2 weeks	TP in pts. in HD	TIN/UFH	●Costs for nursing time were calculated by multiplying nursing time by the average hourly wage for nephrology nurses in Quebec, including social benefits
Pineo,[25] 2011, Canada, USA, Belgium	●Hospital-based costs analyzed ●Using clinical data from PREVAIL;[49] TH: 90 days	TP in pts. with AIS,	ENO/UFH	●Costs: Drug costs and mean Centers for Medicare & Medicaid Services event costs
Wilbur,[26] 2011, Canada	●A decision-analytic model, ●TH: hospital stay: 7 days	TP in hospitalized pts. in medicine	ENO/UFH	●VTE prophylaxis would be initiated for all medical pts. at risk of VTE on day 1 of hospitalization and continued for 7 days
Welsh,[32] 2009, Canada	●A CEA cost-effective analysis; ●Based on ExTRACT-TIMI 25 study[50] ●TH: lifetime	Pts. at fibrinolytic TX for STEMI	ENO/UFH	●All medical costs would be the same except for in the following two aspects: in the 30-day trial, because different treatments were accepted at difference prices and in costs associated with LYL, which is based on the length of LYL and the health expenditure per capita
Studies conducted in non-Canadian settings				
Rothberg,[19] 2012, USA	●Retrospective study ●TH: 2 mos.	TP in pts. with high risk of VTE	LMWH/UFH	●Identity link models were used for analyses of cost ●Cost adjusted for propensity for UFH and other covariates attenuated the association ●Individual pts. were assigned a probability of initial treatment with UFH equal to the hospital rate where they received care
Latour-Perez,[20] 2012, Spain	●Review ●TH: 30 days to 1 year	TP in pts. with ACS	LMWH/UFH	NR
Argenta,[22] 2011, Brazil	Cohort study TH: 2 years	TP in hospitalized pts.	ENO/UFH	NR
Teoh,[23] 2011, USA	●A decision model to evaluate LMWH and UFH for management of postoperative VTE risk	TP in pts. following laparotomy for ovarian cancer	LMWH/UFH	●Costs were based on institutional charges or obtained from the AHRQNIS database for 2008 and average wholesale pricing

First Author, Publication Year, Country	Study Design, Time horizon	Patient Characteristics	Intervention/ Comparators	Assumptions
	TH: I mo.			
Arnold,[27] 2010, USA	●Retrospective study ●TH:1 year	TP in trauma hospitalized pts.	ENO/UFH	NR
Al-Saran,[28] 2010, Saudi Arabia	●Prospective study ●TH: 6 mos.	TP in pts. in HD	TIN/UFH	NR
Bradley,[29] 2010, USA	●Cost-effectiveness model; ● Probabilities and costs were estimated on the basis of published literature and average Medicare reimbursement. ●TH: 21 days	TP in pts. after cancer surgery	LMWH /LDUFH(low dose)	●The risk of VTE or bleeding was constant throughout the 21-day post-discharge period ●Pts. could only have a VTE or a bleeding, not both; ● HIT was followed by thrombosis in most patients, but not bleeding ●All the VTEs and bleeding were treated; ●Any fatal VTEs incurred the same hospital costs as nonfatal VTEs; ● The risk of a post-discharge bleeding event while not receiving TP was zero ●All the available LMWH and pentasaccharide medications were assumed to have the same efficacy and safety
Kadusevicius,[30] 2010, Lithuania	●MA of RCTs ●TH: NR	Pts. in the TX of VTE or pts. with TP	LMWH/UFH	● All studies come from a common population and that the effect size (odds ratio) was not significantly different among the different trials
Menown,[31] 2010, UK	●A CUA using a two-stage model; ●Based on ExTRACT-TIMI 25 study[50] ●TH: lifetime	Pts. at fibrinolytic TX for STEMI	ENO/UFH	●The 10-day median length of hospital stay in ExTRACTTIMI 25 was assumed to include inpatient days required for a reinfarction or revascularization during index hospitalization. ● In the base case analysis, it was assumed the level of disability was severe (i.e., the upper range of costs and lower range of utilities). ●Patients were assumed to be 60 years old at the start of the model (in line with the median age in ExTRACT-TIMI 25), with no patient surviving beyond 100 years, and 12.4% of patients to be over 75 years.
Merli,[33] 2010, USA	●Database analysis ●TH: lifetime	TP in hospitalized pts.	ENO/UFH	●NR
Amin,[17] 2009, USA	Database analysis, using univariate and multivariate model analyses TH: 3 years	TP in pts. at risk of VTE	ENO/UFH	●Hospital utilization charges and costs was tallied over the duration of hospital stay

First Author, Publication Year, Country	Study Design, Time horizon	Patient Characteristics	Intervention/ Comparators	Assumptions
Marcoff,[34] 2009, France	●A CEA ●Based on ExTRACT-TIMI 25 study;[50] ●TH: lifetime	Pts. at fibrinolytic TX for STEMI	ENO/UFH	●The probability assumptions of effectiveness were derived from AHA statistics ●The distributional assumptions of the cost data were based on the actual data in this study, and their ranges come from relevant literature

ACS=acute coronary syndromes; ACT= activated clotting time (ACT); AHA=American Heart Association; AHRQNIS=Agency for Healthcare Research and Quality Nationwide Inpatient Sample; AIS= acute ischemic stroke; CEA=cost-effective analysis; CMA=cost minimization analysis; CUA=cost-utility analysis; DAL=Dalteparin; EA= economic analysis; ENO=enoxaparin; ESRD=End-Stage Renal Disease; ExTRACT-TIMI) 25 study= Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction 25 study; HD=hemodialysis; HIT= heparin-induced thrombocytopenia; ICH=intracerebral hemorrhage; LDUFH=low dose unfractionated heparin; LMWH=low molecular weight heparin; LYL=life years lost; MA=meta-analysis; MO=month; NR: not reported; PREVAIL=Prevention of VTE after Acute Ischemic stroke with LMWH Enoxaparin study; QD= once daily; SR=systematic review; STEMI=ST-Elevation Myocardial Infarction; TH=time horizon; TID=three times daily; TIN=Tinzaparin; TP= thromboprophylaxis; UFH= unfractionated heparin; VTE=venous thromboembolism.

APPENDIX 3: Characteristics of Included Studies for Safety

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention/ Comparator	Clinical Outcomes
Chen,[36] 2013, China	SR (9 RCTs, quasi-RCTs, cohorts, CC and CS studies, 2578 pts)	TP at pts. with SCI	LMWH/ UFH (LDUFH)	●Major bleeding
Costantino,[12] 2012, Italy	SR (27 RCTs, 28637 pts)	TP at pts. with VTE or ACS	LMWH/UFH	●Major bleeding
Junqueira,[13] 2012, Brazil	SR (2 RCTs, 923 pts)	TP at postoperative pts.	LMWH/UFH	●HIT
Sobieraj [37] 2012, USA	SR (7 RCTs, # of pts: NR)	TP in pts. with major orthopedic surgery[a]	LMWH/UFH	●Major bleeding ●HIT
Silvain,[38] 2012, France	SR (23 RCTs or non-RCTs, 30966 pts)	TP in pts. undergoing primary PCI for STEMI or secondary PCI after fibrinolysis	ENO/UFH	●Major bleeding
Kodumuri,[35] 2011, USA	MA (13 RCTs, 12394 pts)	TP in pts. during PCI	LMWH/UFH	●Bleeding
Akl,[39] 2011, Lebanon	SR (16 RCTs, 11847 pts)	Perioperative TP in pts. with cancer	LMWH/UFH	●Bleeding
Buccelletti,[40] 2011, Italy	SR (8 RCTs, 8622 pts)	TP in pts. with STEMI	LMWH/UFH	●Bleeding
Navarese,[41] 2011, multiple countries, USA, Europe	SR (10 RCTs or non-RCTs, 16286 pts)	TP in pts. undergoing PCI for STEMI or secondary PCI after fibrinolysis	LMWH/UFH	●Major bleeding
Phung,[42] 2011, USA	SR (16 RCTs, 27667 pts)	TP in hospitalized non-surgical pts.	LMWH/UFH	●Major bleeding
Laporte,[2] 2011, France	SR (4 RCTs, 3600 pts)	TP in hospitalized medical pts.	ENO/UFH	●Major bleeding
El-Rayes,[43] 2010, Canada	Data-analysis from AMI-QUEBEC registry (498 pts)	TP in medical pts. after fibrinolytic therapy of AMI	ENO/UFH	●Major bleeding
Erkens,[44] 2010, Netherlands	SR (23 RCTs, 4451 pts)	TP in pts. at the TX of VTE	LMWH/UFH	●Major bleeding
Vardi,[45] 2009, Israel	SR (15 RCTs, 3054 pts)	TP in pts. at the TX of VTE	LMWH/UFH (SC)	●Major bleeding
Alikhan,[46] 2009, UK	SR (4 RCTs, 2361 pts)	TP in pts with acute medical illness (excluding stroke and MI)	LMWH/UFH	●Major bleeding
Bump,[47] 2009, Canada, USA	MA (6 RCTs, 3921 pts)	TP in medical pts.	LMWH/UFH	●Bleeding

ACS=acute coronary syndromes; CC= case-control; CEA=cost-effective analysis; CMA=cost minimization analysis; CS=cross-sectional studies CUA=cost-utility analysis; EA= economic analysis; ENO=enoxaparin; HIT= heparin-induced thrombocytopenia; LDUFH=low dose unfractionated heparin; LMWH=low molecular weight heparin; MA=meta-analysis; MI= Myocardial Infarction MO=month;

pts.=patients; PCI= percutaneous coronary intervention; QD= once daily; RCTs=randomized control trials; SC=subscutaneous; SCI=spinal cord injury; SR=systematic review; STEMI= ST-Elevation Myocardial Infarction; TP= thromboprophylaxis; VTE=venous thromboembolism; UFH= unfractionated heparin.
[a] major orthopedic surgery indicated hip replacement, total knee replacement, or hip fracture surgery.

APPENDIX 4: Critical Appraisal of Included Economic Evaluations with Drummond's Checklist[15,16]

First Author, Publication Year, Country	Strengths	Limitations
Studies conducted in Canadian settings		
Thirugnanam,[18] 2012, Canada,	• A rigorous SR of economic analyses • Research question was well defined • The analysis method was clearly stated • The key parameters were justified • The viewpoints in North America settings was stated and justified • Sample size and time horizon was clearly specified • Conflict of interests was declared.	• Some included analysis based on a small # of studies • TH varied widely from study to study (5 days to 8 weeks overall, it was relatively short. Results beyond 8 weeks must be extrapolated carefully • The perspectives varied • Population heterogeneity of included studies with the analysis • Many clinical data based on the radiologic not clinical VTE detection, which may cause of overestimate of the VTE • AE maybe underestimated due to patient with high risk usually excluded in RCT • Assumptions were not clearly reported
Pineo,[21] 2012, (Canada, USA Belgium)	• Research question was well defined • The analysis method was clearly stated • The key parameters were justified • Conflict of interests was declared	• Short TH
Pettigrew,[24] 2011, Canada	• Research question was well defined. • The analysis method was clearly stated • The key parameters on which the analysis was based were justified • The viewpoints in Canadian settings was stated and justified • Sample size and time horizon was clearly specified. • Conflict of interests was declared	• Analysis based on a small sample population • Limitation of generalization due to data collected from one single center
Pineo,[25] 2011, Canada, USA Belgium	• Research question was well defined • The analysis method was clearly stated • The key parameters were justified • Conflict of interests was declared	• Short TH
Wilbur,[26] 2011, Canada	• Research question was well defined • The analysis method was clearly stated • The key parameters on which the analysis was based were justified • The viewpoints in Canadian settings was stated and justified • Sample size and time horizon was clearly specified • Conflict of interests was declared	• from an institutional perspective; not based on the QALY and a societal perspective • Short TH
Welsh,[32] 2009, Canada	• Research question was well defined. • The analysis method was clearly stated • The key parameters on which the analysis was based were justified. • The viewpoints in Canadian settings was	•Assumed that life expectancy after 30 days is similar between ENO and UFH. •the 30-day costs were based on pooled resource use reported in the ExTRACT-TIMI 25 trial, which reflect United States practice patterns for hospitalization and treatment.

First Author, Publication Year, Country	Strengths	Limitations
	stated and justified • Sample size and time horizon was clearly specified. • Conflict of interests was declared.	●the analysis excluded the cost of subsequent CV events from the base-case analysis, due to a lack of information; ●The methodology used may have induced double counting .
Studies conducted in non-Canadian settings		
Rothberg,[19] 2012, USA	• Research question was well defined. • The analysis method was clearly stated • The key parameters were justified. • The viewpoints in USA settings was stated and justified • Conflict of interests was declared.	• Retrospective study prone to selection bias • Administrative data used, certain differences could not be directly adjusted • ENO or UFH may not apply to dosing observed in clinical practice • Outcomes that occurred in the hospital; • TH not clearly reported • Study conducted before the introduction of generic LMWH
Latour-Perez,[20] 2012, Spain	• Research question was well defined • The analysis method was clearly stated • The key parameters were justified • Conflict of interests was declared	• Assumption was not described • Potential underestimation of bleeding costs • TH varies widely
Argenta,[22] 2011 Brazil	• Research question was well defined. • The analysis method was clearly stated • The key parameters were justified • Conflict of interests was declared	● Short TH
Teoh,[23] 2011, USA	• Research question was well defined • The analysis method was clearly stated • The key parameters were justified. • The viewpoints in USA settings was stated and justified • Conflict of interests was declared	●Assumed 100% adherence with each prescription ●Assumed pts. in the LMWH or UFH group also using mechanical device for TP in hospital ●Short TH
Arnold,[27] 2010, USA	• Research question was well defined • The analysis method was clearly stated • The key parameters were justified • The viewpoints in USA settings was stated and justified • Sample size and time horizon was clearly specified • Conflict of interests was declared.	• Retrospective study prone to selection bias • Cost analysis: performed by multiplying the cost of the daily study drug by the total treatment days
Al-Saran,[28] 2010, Saudi Arabia	• Research question was well defined. • The analysis method was clearly stated	• Conflict of interest was declared.
Bradley, [29] 2010, USA	• Research question was well defined. • The analysis method was clearly stated • The key parameters on which the analysis was based were justified. • The viewpoints in USA settings was stated and justified • Sample size and time horizon was clearly specified • Conflict of interests was declared	• Short TH • all the available LMWH and pentasaccharide medications were assumed to have the same efficacy and safety

First Author, Publication Year, Country	Strengths	Limitations
Kadusevicius,[30] 2010, Lithuania	• Research question was well defined • The analysis method was clearly stated • The key parameters were justified • Conflict of interests was declared	●TH not specified
Menown,[31] 2010, UK	• Research question was well defined • The analysis method was clearly stated • The key parameters were justified • Conflict of interests was declared	●Limited quality of the available data
Merli,[33] 2010, USA	• Research question was well defined • The analysis method was clearly stated • The key parameters on which the analysis was based were justified • The viewpoints in USA settings was stated and justified • Sample size and time horizon was clearly specified • Conflict of interests was declared	●Data based on one study
Amin,[17] 2009, USA	• Research question was well defined • The analysis method was clearly stated • The key parameters on which the analysis was based were justified • The viewpoints in USA settings was stated and justified • Sample size and time horizon was clearly specified • Conflict of interests was declared	Data limited in hospital settings
Marcoff, [34] 2009, France	• Research question was well defined • The analysis method was clearly stated • The key parameters on which the analysis was based were justified • Sample size and time horizon was clearly specified • Conflict of interests was declared.	Data based on one study

CV=cardiovascular; ENO=enoxaparin; ExTRACT-TIMI) 25 study= Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction 25 study; LMWH=low molecular weight heparin; TH=time horizon; UFH= unfractionated heparin

APPENDIX 5: Summary of Study Strengths and Limitations (Safety)

First Author, Publication Year, Country	Strengths	Limitations
Chen,[36] 2013, China	• Research questions and selection criteria defined • Two investigators performed selection and DE • List of included studies provided • QA of the included studies described • Publication bias assessed. • Conflict of interests declared	• Only one database searched • List of excluded studies not provided
Costantino,[12] 2012, Italy	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed DE • List of included studies provided • QA of the included studies described • Conflict of interests declared	• List of excluded studies not provided • Publication bias not assessed
Junqueira,[13] 2012, Brazil	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included and excluded studies provided • QA of the included studies described • Conflict of interests declared	• Publication bias not assessed
Sobieraj,[37] 2012, USA	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed DE • QA of the included studies described • Conflict of interests declared	• List of included and excluded studies not provided • Publication bias not assessed.
Silvain,[38] 2012, France	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included studies provided • QA of the included studies described • Conflict of interests declared	• List of excluded studies not provided • Publication bias not assessed.
Kodumuri,[35] 2011, USA	• Research questions and selection criteria were defined	• Publication bias not assessed. • List of excluded studies not provided • QA of the included studies not described • Conflict of interests not declared
Akl,[39] 2011, Lebanon	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included and excluded studies provided • QA of the included studies described • Publication bias assessed. • Conflict of interests declared	None
Buccelletti,[40] 2011, Italy	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included studies provided	• List of excluded studies not provided • QA of the included studies not described • Conflict of interests not declared

	• Publication bias assessed.	
Navarese,[41] 2011, multi-countries, USA, Europe	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed DE • List of included studies provided • QA of the included studies described • Publication bias assessed. • Conflict of interests declared	●List of excluded studies not provided
Phung,[42] 2011, USA	• Research questions and selection criteria defined • Comprehensive search conducted • List of included studies provided • QA of the included studies described • Conflict of interests declared	• List of excluded studies not provided • Publication bias not assessed
Laporte,[2] 2011, France	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included studies provided • QA of the included studies described • Publication bias assessed • Conflict of interests declared	• List of excluded studies not provided
El-Rayes,[43] 2010, Canada	• Research questions and selection criteria defined • Conflict of interests declared	• Comprehensive search not conducted
Erkens,[44] 2010, Netherlands	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included and excluded studies provided • QA of the included studies described • Conflict of interests declared	• Publication bias not assessed
Vardi,[45] 2009, Israel	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included and excluded studies provided • QA of the included studies described • Publication bias assessed • Conflict of interests declared	●None
Alikhan,[46] 2009, UK	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included and excluded studies provided • QA of the included studies described • Conflict of interests declared	• Publication bias not assessed
Bump,[47] 2009, Canada, USA	• Research questions and selection criteria defined • Comprehensive search conducted • Two investigators performed selection and DE • List of included studies provided • QA of the included studies described • Publication bias assessed • Conflict of interests declared	• List of excluded studies not provided

DE= data extraction; QA=quality assessment.

APPENDIX 6: Main Study Findings and Authors' Conclusions (Economics)

First Author, Publication Year, Country	Main Study Findings	Author's Conclusions
Studies conducted in Canadian settings		
Thirugnanam,[18] 2012, Canada	Eight of the 12 studies: LMWH was reported to be the dominant strategy compared with UFH.	On p. 1:" LMWH and fondaparinux are the most economically attractive drugs for venous thromboembolism prevention in hospitalized patients. Approximately two thirds of evaluations were supported by the manufacturer of the new agent; such drugs were likely to be reported as economically favorable."
Pineo,[21] 2012, Canada, USA, Belgium)	Cost/patient (ENO vs. UFH) ● cost per patient due to VTE or bleeding: ENO vs. UFH: $422 vs. $662, net savings $240 for ENO ●Anticoagulant cost per patient: ENO vs. UFH: $360 vs. $259; net savings $101 for UFH ● Total hospital cost per patient: ENO vs. UFH: $782 vs. $922, respectively; savings $140 for ENO); ●Hospital cost-savings were greatest ($287) for ENO in patients with NIHSS scores >/=14.	On p. 176: "The higher drug cost of enoxaparin was offset by the reduction in clinical events as compared to the use of UFH for VTE prophylaxis after AIS, particularly in patients with severe stroke."
Pettigrew,[24] 2011, Canada	●Annual drug costs per patient were CAD 898.56 for tinzaparin and 546.75 for UFH. ●Estimated total annual costs were CAD 1061.03 vs. 1012.71 in the first year and CAD 917.75 vs. 895.23 in subsequent years for tinzaparin vs. UFH, respectively.	On p. 273: "Use of tinzaparin was cost saving relative to UFH if tinzaparin price was reduced 30%. Most of the price differential between tinzaparin and UFH is offset by substantial time savings to nephrology nurses."
Pineo,[25] 2011, (Canada, USA, Belgium)	●Total cost of events and drugs/pt.: ENO vs. UFH: $2018 vs. $2913 and savings of $895 per patient In ENO.	On p. 150: "From a payer perspective, enoxaparin was cost-effective compared with UFH in patients with acute ischemic stroke. The difference was driven by the lower clinical event rates with enoxaparin. Use of enoxaparin may help to reduce the clinical and economic burden of VTE."
Wilbur,[26] 2011, Canada	In the base-case analysis (LMWH –UFH): ● Costs difference (LMWH – UFH): $7.40. ●DVT risk difference (LMWH –UFH): -0.36%; with associated ICERs of $2042; ●Untoward events risk difference: - 0.11%; with associated ICERs of $6832.	On p. 454: "LMWH administration is a cost-effective alternative for TP strategy in Canadian hospitalized medicine patients."
Welsh,[32] 2009, Canada	●ENO vs. UFH (during 30 days) - death or recurrent MI rate 9.9% vs. 12.0%, P<0.001. (less in ENO) -cost: $8,757.00 vs. $8,587.50; cost $169.50 more in ENO) ● Life years gained: increased by 0.11 years (P<0.05) in ENO vs. UFH; ● ICER: ENO found to be cost-effective, as indicated by an ICER of $4,930 with a 99% probability of costing less than $20,000.	On p. e399: "Although associated with modest increased direct medication costs, enoxaparin following fibrinolysis improved the clinical efficacy in STEMI patients and increased the life years gained."
Studies conducted in non-Canadian settings		
Rothberg,[19] 2012, USA	OR (95%CI): (UFH vs. LMWH) VTE: 1.14 (0.72-1.81); Major bleeding: 1.64(0.50-5.33) Cost ratio: 0.97 (0.90-1.05)	On p. 457: "For VTE prophylaxis, the effectiveness and cost of LMWH and UFH are similar, but LMWH is associated with fewer complications."
Argenta,[22] 2011, Brazil	UFH vs. ENO ●# of bleeding events: (10.0% vs. 9.4%; P =	On p. s89: "The treatment of VTE with enoxaparin provided cost savings in a large teaching hospital

First Author, Publication Year, Country	Main Study Findings	Author's Conclusions
	1.00, NS); ●blood transfusion (2.0% vs. 2.6%; P = 1.00); ●death (8.0% vs. 3.4%; P = 0.24); and ●recurrent VTE, bleeding, or death (20.0% vs. 14.5%; P = 0.38). ●Daily mean cost per patient was US$12.63 ± $4.01 for UFH and US$9.87 ± $2.44 for ENO (P < 0.001). ●The total costs considering the mean time of use were US$88.39 for UFH and US$69.11 for ENO.	located in southern Brazil."
Teoh,[23] 2011, USA	●In the base case, UFH (1 mo.) was the least expensive (mean cost $1611) and most effective (VTE risk 1.9%) strategy. LMWH (1 mo.) was equally effective but more expensive ($2197). ●Inpatient UFH (5000 units, TID) and inpatient LMWH (40mg, QD), were less effective and more expensive than UFH (1 mo.).	On p. 467: "Based on current evidence, extended prophylaxis with UFH is the least expensive and most effective strategy to prevent postoperative VTE following laparotomy for ovarian cancer."
Arnold,[27] 2010, USA	●PLE DVTs: ENO vs. UFH: 16 (6.75%) vs. 17 (7.11%) (P = 0.999); ●PE and bleeding: ENO vs. UFH: NS; ●Extrapolated yearly pharmacy cost savings of $135,606 in UFH compared with ENO.	On p. 563: "In trauma patients, subcutaneous heparin dosed three times a day may be as effective as standard-dosed enoxaparin for prophylaxis of venous thromboembolism without increased complications. Heparin three times a day for venous thromboembolism prophylaxis was associated with significant pharmaceutical cost savings."
Al-Saran,[28] 2010, Saudi Arabia	●TIN resulted in less frequent dialyzer and air-trap clotting compared to UFH (P= 001 and 0.04 respectively); ●The total cost for 24 weeks use of tinzaparin sodium was 23% more expensive compared to that for UFH.	On p. 43: "A single bolus of Tinzaparin sodium injection at the start of the dialysis session was more effective and convenient in our patients than UFH, but at a higher total cost."
Bradley,[29] 2010, USA	●Annual population cost relative to no prophylaxis in USA (baseline analysis) LDUH: - $30.3 million vs. LMWH: 81.9; ●Cost-effectiveness relative to no prophylaxis: when medication compliance is considered: LDUH: - $76 vs. LMWH: 325; ● Cost-effectiveness relative to no prophylaxis (for only symptomatic VTEs are identified and treated) LDUH: $185 vs. LMWH: 873;	On p. 31: "Although all chemical prophylaxis is effective in preventing VTE in the outpatient setting after cancer surgery, either LDUH or aspirin are the most cost-effective, depending on patient compliance."
Kadusevicius,[30] 2010, Lithuania	●In comparison to UFH, all LMWH have independently demonstrated greater safety and effectiveness; ●Introduction of reference pricing for LMWH would decrease the total expenditure on LMWH of approximately 30 percent and would result in total savings of 1.830-2.070 thousand LTL (approximately 0.8 million USD) per year.	On p. 272: "The meta-analysis results of LMWH could be used to support a policy on reference-based pricing and pharmacoeconomic decision modeling in healthcare institutions, which would allow a decrease in healthcare expenditures."
Menown,[31] 2010, UK	●Assuming treatment continuation for 7 days, the mean day 1-30 incremental cost associated with enoxaparin was £49 per patient, and mean lifetime incremental cost was £592 per patient (£ 91,091 vs. £90,499, respectively). ●Given an additional 0.048 life years gained	On p. 181: "The use of an enoxaparin versus UFH strategy in patients receiving fibrinolytic therapy for STEMI, whether continued for 7 days or discontinued early, for example following urgent revascularization, is cost effective at a pound 20,000 willingness-to-pay threshold."

First Author, Publication Year, Country	Main Study Findings	Author's Conclusions
	per patient with enoxaparin, the cost per life year saved was £12,353, and given an additional 0.038 QALYs per patient with enoxaparin, the cost per QALY was £15,413. ●In an alternative scenario, reflecting contemporary practice assuming early treatment discontinuation at 48 hours, for example following urgent revascularization, the incremental cost per QALY was £ 13,556.	
Merli,[33] 2010, USA	●Adjusted mean difference of total direct medical costs per discharge (ENO-UFH): - $1,080 (P < 0.0001).	On p. 449: "enoxaparin prophylaxis is a cost-saving therapy, when compared with UFH, for the prevention of VTE in patients with a diverse range of medical conditions conferring VTE risk."
Amin,[17] 2009, USA	(ENO vs. UFH) OR (95%CI): ●VTE: OR 0.51 (0.30-0.86) p = 0.012; ●PE: OR 0.33 (0.14-0.79) p = 0.013; ●Total hospital costs per discharge: ENO: US $16,865±10,979 than UFH (US $19,252± 14,970, mean difference: US $2,388 in favor of ENO (p < 0.001) (adjusted difference US $439 (-39 to 909) p = 0.072)	On p. 321:" In patients at risk of VTE, appropriate enoxaparin prophylaxis was associated with a reduction in hospital-acquired VTE, adverse events, and costs compared with appropriate UFH prophylaxis. Increased appropriate use of enoxaparin in patients at risk of VTE may help to reduce the clinical and economic burden of this condition."
Marcoff,[34] 2009, France	●Index hospitalization costs: difference: (ENO-UFH) - $126; (95% CI: -$295 to $49). ●Thirty-day costs: (ENO-UFH) $102 (95% CI: $108 to $314); ● life-years gain difference (ENO-UFH): 0.12; ● Estimated total lifetime costs (ENO-UFH): $1,207 (95% CI: $491 to $1,923). ● The ICER: (ENO vs. UFH): $5,700 per life-year gained, with 99.9% of bootstrap-derived estimates <$50,000 per life-year gained. ●Using a probabilistic sensitivity analysis, there is a 90% probability that ENO is cost effective for lifetime, provided that the WTP value exceeds $50,000.	On p. 1271: "Based on a U.S. model of health care economics, the strategy of using enoxaparin instead of UFH as adjunctive therapy for fibrinolysis in patients with STEMI is cost effective according to commonly used benchmarks."

CI=confidence interval; DVT=deep venous thrombosis; ENO=enoxaparin; ICER= increased cost effectiveness ratio; LDUH=low dose unfractionated heparin; LTL=Lithuanian litas; LMWH=low molecular weight heparin; MI=myocardial infarction; NIHSS scores= National Institutes of Health Stroke Scale (NIHSS) classification scores (<14 or 14) NS=not statistically significant; OR=odds ratio; PE= pulmonary embolism; PLE=proximal lower extremity; QALY=quality-adjusted life years; QD= once daily; RR=relative risk; STEMI=ST-Elevation Myocardial Infarction; TID=three times daily; TIN=Tinzaparin; TP= thromboprophylaxis; TX=treatment; UFH= unfractionated heparin; VTE=venous thromboembolism; WTP= willingness-to-pay.

APPENDIX 7: Main Study Findings and Authors' Conclusions (Safety)

First Author, Publication Year, Country	Main Study Findings	Author's Conclusions
Chen,[36] 2013, China	Major bleeding: RR (95%CI) (LDUH vs. LMWH) 2.034 (1.018 to 4.063) P=0.044 (in favor of LMWH)	On p. e44553: "Our meta-analysis showed that in patients with acute SCI, LDUH have no TP effect compared with placebo or untreated; LMWH seems only can reduce bleeding incidence, but not prophylaxis thromboembolism compared with LDUH. Because of no good quality studies existed in this setting, well-designed RCTs are urgently needed."
Costantino,[12] 2012, Italy	Major bleeding: OR (95%CI) (LMWH vs. UFH) ●Overall: 0.79 (0.60 to1.04) ●In VTE: 0.68 (0.47 to 1.00)	On p.1: "The results of our systematic review suggest that the use of LMWH in the treatment of VTE might be associated with a reduction in major bleeding compared with UFH. The choice of which heparin to use to minimize bleeding risk must be based on the single patient, taking into account the bleeding profile of different heparins in different settings."
Junqueira,[13] 2012, Brazil	HIT: RR (95%CI) (LMWH vs. UFH) 0.24 (0.07 to 0.82) P = 0.02;	On p. 2: "There was a lower incidence of HIT and HIT complicated by VTE in postoperative patients undergoing TP with LMWH compared with UFH. This is consistent with the current clinical use of LMWH over UFH as front-line heparin therapy. However, conclusions are limited by a scarcity of high quality evidence…"
Sobieraj,[37] 2012, USA	OR (95%CI) (LMWH vs. UFH) ●Major bleeding: 0.57 (0.37 to 0.88) ●HIT: 0.12 (0.03 to 0.43)	On p 800: "According to moderate-to-high strength of evidence, LMWH prophylaxis provides additional benefits with less harm compared with UFH…"
Silvain,[38] 2012, France	RR (95%CI) (LMWH vs. UFH) Major bleeding: 0.80 (0.68 to 0.95) P=0.009	Con p. 1: "Enoxaparin seems to be superior to unfractionated heparin in reducing mortality and bleeding outcomes during percutaneous coronary intervention and particularly in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction."
Kodumuri,[35] 2011, USA	RR (95%CI) (LMWH vs. UFH) ●bleeding: 0.79 [0.59 to 1.05]; ●bleeding using IV or intra-arterial LMWH subgroup: 0.63 (0.48 to 0.82).	On p. 180: "LMWH is at least as efficacious and safe as UFH in patients undergoing PCI. Additionally, evidence suggests that LMWH, when used intravenously, is associated with lower bleeding risks when compared with UFH."
Akl,[39] 2011, Lebanon	RR (95%CI) (LMWH vs. UFH) ● minor bleeding : 0.88 (0.47 to 1.66 ●major bleeding 0.84 (0.52 to 1.36)	On p. 2: "We found no difference between perioperative TP with LMWH versus UFH in their effects on mortality and embolic outcomes in patients with cancer. Further trials are needed to more carefully evaluate the benefits and harms of different heparin TP strategies in this population."
Buccelletti,[40] 2011, Italy	Bleeding: OR (95%CI) (LMWH vs. UFH) 1.40 (0.80 to 2.47); NS.	On p. 701: "Compared to placebo or UFH, LMWH is effective as a first line treatment of STEMI patient with no significant increase in major hemorrhagic events."
Navarese,[41] 2011, multi-countries, USA, Europe	RR (95%CI) (LMWH vs. UFH) ●Major bleeding in primary PCI: 0.68 (0.49 to 0.94) P=0.02 ●Major bleeding in secondary PCI after thrombolysis: 0.91 (0.66 to 1.25) P=0.56	On p. 1902: "LMWH were associated with greater efficacy and safety than UFH in STEMI patients treated with pPCI, with a significant relationship between risk profile and clinical benefits. Based on this meta-analysis, LMWH may be considered as a preferred anticoagulant among STEMI patients undergoing pPCI."
Phung,[42] 2011, USA	RR (95%CI) (LMWH vs. UFH) ● major bleeding : 0.89 (0.08 to 7.05)	On p. 374: "Moderate-quality evidence suggests that subcutaneous UFH bid and UFH tid. do not differ in effect on DVT, PE, major bleeding, and mortality. Either of the two dosing regimens of UFH or LMWH appears to be a reasonable strategy for thromboprophylaxis in medical patients. A future randomized trial comparing the two

		doses of UFH is very unlikely, considering the very large sample size that would be required to demonstrate a significant difference, which, if it exists, is undoubtedly small."
Laporte,[2] 2011, France	RR (95%CI) (LMWH vs. UFH) ● major bleeding : 1.13 (0.53 to 2.44); P=0.75	On p. 464: "Enoxaparin significantly reduces VTE in hospitalized medical patients, compared with UFH, without increasing the risk for major bleeding, and was associated with a trend towards reduced all-cause mortality."
El-Rayes,[43] 2010, Canada	LMWH vs. UFH ● Major bleeding: 4.4% vs. 6%, P=0.51.	On p. 431: "INTERPRETATION: There was no significant difference in the rates of in-hospital adverse events in the ENOX group compared with the UFH group, when used in the real-life context. Larger observational studies may further confirm the safety, effectiveness and optimal duration of the administration of ENO in unselected STEMI patients treated with fibrinolysis."
Erkens,[44] 2010, Netherlands	OR (95%CI) (LMWH vs. UFH) ● major bleeding at initial TX : 0.58 (0.40 to 0.83); P=0.003; ● major bleeding at the end of F/U: 0.50 (0.29 to 0.85); P: NR	On p. 2: "Fixed dose LMWH is more effective and safer than adjusted dose UFH for the initial treatment of VTE. Compared to UFH, LMWH significantly reduced the incidence of thrombotic complications, the occurrence of major hemorrhage during initial treatment and overall mortality at follow up."
Vardi,[45] 2009, Israel	OR (95%CI) (LMWH vs. UFH) ● major bleeding during TX: 1.07 (0.64 to 1.79); (NS) ● major bleeding at F/U of 3 mos.: 0.66 (0.33 to 1.32); (NS)	On p. 2: "Subcutaneous unfractionated heparin for the treatment of venous thromboembolism cannot be considered non-inferior to other treatment modalities in terms of recurrent DVT and PE at three months, but seems as safe and effective with regards to rates of major bleeding and death."
Alikhan,[46] 2009, UK	RR (95%CI) (LMWH vs. UFH) ● Major bleeding: 0.28 (0.10 to 0.78); P=0.02. ●minor bleeding: 0.40 (0.08 to 2.10); P=0.02	On p. 2: "… Although the analysis found no significant difference in efficacy between LMWH and UFH, it did note differences in the incidence of DVT and clinical PE with a significantly reduced risk of bleeding in favor of LMWH."
Bump,[47] 2009, Canada, USA	RR (95%CI) (LMWH vs. UFH) ● Major bleeding: 0.57 (0.25 to 1.32) ●Any bleeding: 0.72 (0.44 to 1.16)	On p. 1289: "…The current literature does not demonstrate superior efficacy of UFH or LMWH."

CI=confidence interval; DVT=deep venous thrombosis; ENO=enoxaparin; F/u=follow up; HIT= heparin-induced thrombocytopenia; LDUH= low-dose unfractionated heparin; LMWH=low molecular weight heparin; NR=not reported; NS=not statistically significant; PCI= percutaneous coronary intervention; PE=pulmonary embolism; pPCI= primary percutaneous coronary intervention; OR=odds ratio; RR=relative risks; STEMI=ST-Elevation; TIN=Tinzaparin;TP= thromboprophylaxis UFH=unfractionated heparin; TX: treatment; VTE=venous thromboembolism.