ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Low-molecular-weight heparins (LMWH) for the treatment and secondary prevention of venous thromboembolism (VTE)

FINAL PHARMACOECONOMICS REPORT

April 2016

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the low-molecular weight heparin drug class review.

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Study Team

Pharmacoeconomics Team: Doug Coyle, Karen Lee, Mirhad Lončar, Kathryn Coyle

Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Briefing

- This report assessed the current evidence regarding the comparative cost-effectiveness of low molecular weight heparins (LMWH) in the treatment and secondary prevention of venous thromboembolism in patients with cancer.

- The availability of well-conducted independent economic analyses from the Canadian perspective is currently lacking in the published literature. Three economic evaluations which addressed our research questions were identified; however, two studies received funding from the pharmaceutical industry which potentially affects the interpretation of the results. As such, a de novo model was developed focusing on the prevention of recurrent VTE in cancer patients.

- A de novo economic model was developed to assess the cost-effectiveness of LMWH medications compared with warfarin in the secondary prevention of cancer-related VTE. A decision tree model was developed and adapted to allow incorporation of effectiveness data from two different sources, modeling the impact of treatment over a 6-month period.

- In patients with cancer diagnosed with a VTE, long term prophylaxis with LMWH was not cost-effective in comparison with warfarin prophylaxis based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained.

List of abbreviations	
CAD	Canadian dollar
CEA	cost-effectiveness analysis
CLOT	**C**omparison of **L**ow molecular weight heparin versus **O**ral anticoagulant **T**herapy for long term anticoagulation in cancer patients with venous thromboembolism (trial)
CMA	cost-minimization analysis
CUA	cost-utility analysis
DC	Doug Coyle
DVT	deep vein thrombosis
HCP	health care payer
ICER	incremental cost-effectiveness ratio
INR	international normalized ratio
IU	International Unit
LMWH	Low-molecular-weight heparin
ML	Mirhad Lončar
PE	pulmonary embolism
QALY	quality-adjusted life year
RCT	randomized controlled trial
USA	United States
USD	US dollar
VTE	venous thromboembolism

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Executive Summary

Research Questions

RQ1a. What is the current evidence for the comparative cost-effectiveness of low-molecular weight heparins (LMWH), as compared with each other, warfarin, parenteral anticoagulation or placebo, for the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer?

RQ1b. What is the current evidence for the comparative cost-effectiveness of low-molecular weight heparins (LMWH), as compared with each other, warfarin, parenteral anticoagulation or placebo, for the secondary prevention of DVT or PE in patients with cancer?

RQ2. Based on a de novo economic model, what is the comparative cost-effectiveness of LMWH, as compared with warfarin, for the prevention of DVT or PE in patients with cancer?

Systematic Review of Published Economic Evaluations

In brief, this review highlights the current published evidence on the comparative cost-effectiveness of pharmacologic treatments in the initial management and secondary prevention of VTE in cancer patients. Three published economic evaluations which addressed the research questions of the review were identified; two studies focused on the secondary prevention of cancer-related VTE, while one study assessed the comparative cost-effectiveness of therapies in the initial management (treatment) of DVT in cancer patients. Two of three included studies cited financial support from the pharmaceutical industry, and results of these studies favoured the sponsor's product. The paucity of well conducted independent analysis from the Canadian perspective precluded any inferences regarding the cost-effectiveness of LMWH medications in the treatment or secondary prevention of cancer-related VTE.

Of the three published economic evaluations identified in this review (two cost-effectiveness/cost-utility analyses and one cost-minimization analysis), two analyses were conducted in the United States and one in Canada. The two cost-effectiveness/cost-utility analyses differed in their approach to modeling costs and benefits associated with chosen treatment comparators: one study adopted a trial-based analysis based on the Canadian CLOT trial, while the other study used a decision-tree model. The cost-minimization analysis assumed equal efficacy between all modeled treatment and reported the findings in terms of cost savings. In addition to the receipt of industry funding, the main limitations among included studies relate to unsupported assumptions regarding the impact of LMWH on patients' survival, or the approach to eliciting utility values from patient surrogates in the case of the Canadian study. Moreover, the publication date of these economic analyses is unlikely to reflect the current clinical evidence base and cost data.

Given the shortcomings associated with the published literature, which limit the applicability and generalizability of the results, a de-novo economic model which incorporates relevant evidence form the Canadian context is required to assess the comparative cost-effectiveness of this drug class.

For a detailed report of the review of economic literature regarding this drug class, refer to Appendix A – Systematic Review of Economic Evidence.

De novo Economic Evaluation

A de novo decision analytic economic model was developed to assess the cost-effectiveness of LMWH versus warfarin for the prevention of recurrent VTEs. The model structure was adapted from Aujesky et al. (2005).[1] Two analyses were conducted. In the first case, the model was populated with data from the CLOT clinical trial which compared a LMWH, dalteparin, with warfarin treatment over a 6-month period in patients diagnosed with cancer who had experienced a VTE. Outcomes included the rate of recurrence of VTEs (DVTs or PEs), major bleeds, minor bleeds and mortality. In the second analysis, the model was adapted to allow the relative risk of events (DVTs, major bleeds, minor bleeds and death) with LMWH from a Cochrane meta-analysis to be applied to the probabilities of the warfarin arm of the CLOT trial to estimate the comparative cost-effectiveness of treatments.[2] Resource use was estimated based on the results of the CLOT clinical trial and costs were sourced from established Canadian references.[3-10] Utilities associated with each of the states within the model were derived from the literature.[11-13] Analysis was conducted from the perspective of the Ontario Ministry of Health with results presented as incremental cost per quality-adjusted life years (QALY) gained. The impact of alternative assumptions regarding parameter estimates and model structure were tested through deterministic sensitivity analyses. Detailed probabilistic sensitivity analysis was performed to assess decision uncertainty.

Long-term (6-month) prophylaxis against recurrent VTE with LMWH results in slightly greater QALYs compared with warfarin; however, the costs associated with LMWH are significantly greater than warfarin. The incremental cost effectiveness ratio (ICER) for LMWH versus warfarin is greater than $1 million per QALY gained.

These results were found to be robust to alternative assumptions regarding input parameters for costs, resources, utilities and model structure with the ICER ranging from $175,000 to $2.4 million per QALY with LMWH versus warfarin.

In probabilistic sensitivity analyses, LMWH was found to be more effective than warfarin in approximately 70% of replications, but it was found to be more costly in 100% of replications. The probability that LMWH is cost effective at a willingness to pay per QALY value of both $50,000 and $100,000 was zero.

In patients with cancer diagnosed with a VTE, long-term prophylaxis with LMWH was not cost-effective as compared with warfarin prophylaxis. The ICER for LMWH versus warfarin was greater than $1 million per QALY.

Appendices

Appendix A – Systematic Review of Economic Evidence

Research Questions

RQ1a. What is the current evidence for the comparative cost-effectiveness of low-molecular weight heparins (LMWH), as compared with each other, warfarin, mechanical intervention, parenteral anticoagulation or placebo, for the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer?

RQ1b. What is the current evidence for the comparative cost-effectiveness of low-molecular weight heparins (LMWH), as compared with each other, warfarin, mechanical intervention, parenteral anticoagulation or placebo, for the secondary prevention of DVT or PE in patients with cancer?

Review of Published Literature

Search Strategy and Search Findings

Search Strategy

A search of the medical literature was conducted in Ovid MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE ® from 1946 to present (2015 November 17) as well as EMBASE 1980 to present (2015 November 17) in order to capture all relevant literature. Key words relating to LMWH treatments approved for use in Canada (dalteparin, enoxaparin, nandroparin, tinzaparin, fondaparinux) were coupled with a standardized search strategy for identifying economic analyses adopted by the National Health Service Economic Evaluation Database (NHS EED). The complete search strategy can be found in Appendix A1: Search Strategy.

Additional citations were retrieved for screening from the Tufts CEA Registry and NHS EED databases. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE) websites. Finally, reference lists of included studies were hand searched for additional relevant records.

Search Findings

A total of 201 citations relating to the cost-effectiveness of treatments for the treatment (initial management) and/or secondary prophylaxis of VTE in cancer patients were identified from the initial searches, 152 of which were found through searches of electronic databases and an additional 49 records identified from grey literature sources. Following the removal of duplicate records, 189 unique citations were retrieved for screening.

Two reviewers (ML and DC) independently reviewed the titles and abstracts of studies identified by the search strategy in order to identify potential articles for critical appraisal. Namely, of the 189 unique records screened, 28 citations were selected for full-text review.

Thus, a total of 161 records were excluded in the first phase of screening, and an additional 25 records were excluded following assessment of full-text articles. Any disagreements during this two-stage screening process were resolved through consensus. Exhibit 1 in Appendix A2 presents the search results, including reasons for exclusion of full-text publications.

Among the 28 articles that were retrieved for full-text review, a total of 3 studies addressed the objective of the review and were selected for inclusion. No additional potentially relevant studies were identified from hand-searching citations of included papers or manufacturer submissions. A list of excluded studies along with reasons for exclusion is presented in Exhibit 2 of Appendix A3.

Included Studies

A list of included studies is presented in Exhibit 3 of Appendix A4.

Summary and Critical Appraisal of Included Studies

Included Studies

A total of three published economic evaluations which examined the comparative cost-effectiveness of treatments for the initial management or secondary prevention of VTE in cancer patients were included in this review; two studies focused on the secondary prophylaxis of cancer-related VTE,[1,14] while one study assessed the initial management of DVT in cancer inpatients.[15] Of the included studies, two were conducted in the United States[1,15] and one in Canada.[14] In addition, two studies received direct sponsorship from the pharmaceutical industry,[14,15] and one study was independently funded.[1] A brief overview of the characteristics of these three economic analyses in presented in Exhibit 4 of Appendix A5.

Two of the economic evaluations assessed the cost-effectiveness of therapies for the secondary prevention or recurrence of VTE in cancer patients using a cost-effectiveness/cost-utility analysis.[1,14] One study used a decision tree for estimating costs and outcomes relating to treatment with either subcutaneous dalteparin in comparison with warfarin;[1] and, the other study compared the same two treatments using a trial-based analysis.[14] Furthermore, both economic analyses modeled disease progression among adult cancer patients who experienced a recurrent venous thromboembolic event. While one analysis adopted a lifetime time horizon,[1] the time frame in the second study was unclear.[14]One study was conducted from perspective of the Canadian health care payer, while the other evaluation was conducted from the United States societal perspective.

In addition to the two cost-effectiveness/cost-utility studies, there was one cost-minimization analysis.[15] This study examined the cost savings associated with the use of subcutaneous dalteparin in comparison with unfractionated heparin for the initial treatment of cancer inpatients with acute DVT. The analysis adopted a health care payer perspective, and the duration of treatment (approximately one week) comprised the study's time horizon.

Study outcomes for the two studies which assessed cost-effectiveness of therapies for the secondary prevention of cancer-related VTE were expressed as incremental costs per quality-adjusted life years (QALY) gained and/or incremental costs per VTE avoided. Conversely, the

outcome associated with the initial management of a venous thromboembolic event, as evaluated by the cost-minimization analysis, was expressed as mean costs of inpatient care for each treatment comparator. Moreover, of the two economic analyses which measured patients' health related-quality of life, one study derived utility estimates from the published literature, while the other elicited utilities using the time trade-off technique among 24 oncology care providers who acted as patient surrogates. A detailed synthesis of the interventions and results of the three included economic evaluations is presented in Exhibit 5 of Appendix A5.

Considerations and Limitations Relating to the Literature

A number of limitations relating to the available cost-effectiveness evidence may reduce its usefulness in addressing the research questions for this review. A brief summary of these issues is presented below.

Paucity of Evidence

There is a lack of well conducted published studies relating to the cost-effectiveness of LMWH medications in the treatment or secondary prevention of cancer-related VTE. Three studies met the inclusion criteria for this review, one of which focused on the cost-effectiveness therapies for the initial management of VTE in cancer patients.

Canadian Content

There was one economic evaluation which examined the comparative cost-effectiveness of LMWH treatment in cancer patients with recurrent VTE from a Canadian perspective. However, this study is funded by the pharmaceutical industry (potential bias) and the age of the study does not reflect the current clinical evidence base or cost data, which limits its use in aiding decision making.

Sponsorship and Industry Affiliated Studies

Two of the three studies included in this review reported receiving financial support from pharmaceutical manufacturers.[14,15] These studies may be susceptible to biases and limitations that have been found in manufacturer-sponsored evaluations.[16]

Canadian Studies

There was one study which examined the comparative cost-effectiveness of LMWH versus warfarin for the secondary prophylaxis of cancer-related VTE. An overview of this study and its limitations is provided below.

Dranitsaris et al. (2006)

Dranitsaris et al. conducted a cost-effectiveness/cost-utility analysis comparing subcutaneous dalteparin with vitamin K antagonist warfarin (target INR 2.5) in the secondary prevention of VTE in cancer patients; dalteparin was administered at 200 IU/kg once daily in the first month, then 150 IU/kg per day from months 2 to 6. This economic evaluation was a trial-based analysis, and the time horizon adopted in the analysis was unclear. Data on resource use and treatment efficacy was sourced from a single, Canadian randomized controlled trial (CLOT

trial [Comparison of Low molecular weight heparin versus Oral anticoagulant Therapy for long term anticoagulation in cancer patients with venous thromboembolism]).[17] Cost estimates relating to anticoagulant medications, diagnostic test, unscheduled patient contact, blood transfusions, and treatment of VTE and other events were included in the base-case analysis. Utility estimates were based on the responses from 24 oncology care providers, acting as patient surrogates, using the time trade-off (TTO) technique. Study outcomes were reported as incremental costs per VTE avoided, as well as incremental costs per quality-adjusted life year (QALY) gained. The analysis was conducted from the perspective of the Canadian health care payer, with all costs presented in 2005 Canadian dollars.

Base-case results showed that treatment with dalteparin was associated with $27,700 per VTE avoided, as compared with warfarin. Subcutaneous dalteparin was further associated with an ICER of $13,751 per QALY gained in comparison with oral therapy. Study finding were subject to a one-way sensitivity analysis, which showed that the ICER estimate was robust to changes in model assumptions. As a result, the authors concluded that long-term dalteparin therapy was a cost-effective therapy, as compared with warfarin, for the prevention of recurrent VTE in cancer patients.

Overall, while this study adopted the Canadian perspective, its applicability within the current decision making setting remains limited. This is mainly due to shortcomings in the way utility values were derived (i.e. non-validated method using patient surrogates, as described above), and the trial-based nature of the analysis which limits its generalizability to settings outside of that in which the trial was conducted. In addition, within the utility assessment, the assumption was made that survival would be greater with dalteparin than with warfarin. This was based on data relating to a subset of patients with non-metastatic solid tumors. Within the wider population of the CLOT trial, there was no treatment-related difference in survival. This study is also funded by the pharmaceutical industry, and the date of the study (2006) is unlikely to reflect the current clinical evidence base and cost data.

Non-Canadian Studies

Independent studies

Aujesky et al. (2005)

Aujesky et al. examined the comparative cost-effectiveness of subcutaneous dalteparin versus warfarin in the secondary prevention of VTE in cancer patients. Similarly to the Dranitsaris et al. (2006) study, dalteparin was administered subcutaneously at 200 IU/kg once daily within the first month of treatment, then at 150 IU/kg per day for months 2-6; warfarin oral therapy was dosed at the target international normalized ratio of 2.5, and patients received both treatment for a total of six months. Unlike the trial-based Dranitsaris et al. study, this cost-effectiveness/cost-utility analysis was based on a decision tree model and run over a lifetime time horizon. Efficacy data were sourced from the Canadian CLOT trial,[17] including information on the probabilities of early complications, mortality rates, recurrent VTE, and major bleeding episodes; data for uncommon complications were derived from a published meta-analysis. The analysis was conducted from the perspective of the United States health care payer and societal perspectives, incorporating costs of hospitalization, emergency department and physician visits, home nursing care, laboratory tests, medical procedures, as

well as indirect patient costs; all costs were presented in 2002 US dollars. Utility values were sourced from the published literature, and the final outcomes of the analysis were reported at incremental costs per life-year gained, as well as incremental costs per QALY gained.

Results of the base-case analysis revealed that treatment of recurrent VTE with dalteparin in cancer patients generated an ICER of $149,865 per QALY gained when compared with warfarin (1.00 USD = 1.59 CAD; 2002); the unadjusted ICER for dalteparin versus warfarin was $115,847 per life-year gained. Deterministic sensitivity analyses revealed that study results were sensitive to early mortality rates associated with both comparators, daily pharmacy costs for dalteparin, utility estimates, the need for nursing care, and early risks for recurrent VTE or bleeding episodes. Probabilistic sensitivity analysis showed that warfarin was more cost-effective than dalteparin in 97% of Monte-Carlo iterations at a willingness-to-pay threshold of $50,000/QALY gained.

Overall, while this study appeared well designed and while the applicability of the study is strengthened by the absence of industry sponsorship, certain factors may limit its use in aiding decision-making. Specifically, the authors assumed that treatment with LMWH would result in patients' increased survival, as compared with warfarin, and that most of the benefit associated with LMWH was due to this presumed survival benefit; yet, this assumption remains unsupported by clinical evidence and ultimately precludes a clear interpretation of the results. In addition, given the date of the study (2005), current clinical evidence and cost data are unlikely to be reflected.

Industry-sponsored or industry-affiliated studies

There was one economic evaluation conducted outside of Canada which received financial support from the pharmaceutical industry. This study, conducted with Avritscher et al. in 2004, was a cost-minimization analysis sponsored by Pharmacia, and focused on the initial management of VTE in cancer inpatients. Similar to other industry-sponsored studies, results of this economic analysis favoured the sponsor's product.

Overall Conclusions

On the whole, there is a lack of available evidence relating to the comparative cost-effectiveness of pharmacologic treatments for the initial management and/or secondary prevention of VTE in cancer patients.

Cost-effectiveness evidence suggests that well-designed independent analyses from the Canadian perspective are lacking; as a result, de novo modeling is required to address this evidence gap.

Appendix A1: Search Strategy

The following search strategy was applied in Ovid MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE ® from 1946 to present (2015 November 17) as well as EMBASE 1980 to present (2015 November 17) to identify health economic studies relating to the pharmacologic treatment or secondary prevention of VTE in cancer patients.

1 exp Heparin, Low-Molecular-Weight/
2 LMWH.tw,kw.
3 ((low molecular weight or LMW) adj1 heparin).tw,kw.
4 Heparin, Low-Molecular-Weight.rn.
5 (Dalteparin* or FR-860 or Fragmin or Fragmine or Kabi-2165 or "K 2165"' or K2165 or Tedelparin or low liquemin).tw,kw.
6 dalteparin.rn.
7 (Enoxaparin* or Clexan* or EMT-966 or EMT-967 or HSDB 7846 or Klexane or Lovenox or PK10169 or PK 10169 or "PK-10,169" or RP 54563 or UNII-8NZ41MIK1O).tw,kw.
8 enoxaparin.rn.
9 (nadroparin* or CY 216 or CY 216d or CY216 or CY216d or Fraxiparin* or LMF CY-216 or Nadroparin Calcium or Nadroparine or Nadrohep or Fraxodi or Seleparin* or Tedegliparin*).tw,kw.
10 nadroparin.rn.
11 (tinzaparin* or Innohep or UNII-7UQ7X4Y489).tw,kw.
12 tinzaparin.rn.
13 (bemiparin* or hibor or phivor or ardeparin* or UNII-N3927D01PB).tw,kw.
14 (certoparin* or Alphaparin* or Alpha-parin* or Mono-Embolex or Monoembolex).tw,kw.
15 (Reviparin* or Clivarin* or LU 47311 or LU47311 or lomorin).tw,kw.
16 reviparin.rn.
17 (parnaparin* or parvoparin* or fluxum or lohepa or lowhepa or minidalton or op 2123 or CB-01-05-MMX).tw,kw.
18 Parnaparin.rn.
19 (semuloparin* or mulsevo or visamerin or AVE 5026 or AVE5026 or UNII-4QW4AN84NQ).tw,kw.
20 semuloparin.rn.
21 sevuparin*.tw,kw.
22 sevuparin.rn.
23 (ardeparin* or normifio or normiflo or rd heparin or wy 90493 or wy90493).tw,kw.
24 ardeparin.rn.
25 (adomiparin* or "m 118" or m118).tw,kw.
26 adomiparin.rn.
27 ("cy 222" or cy222).tw,kw.
28 cy 222.rn.
29 (danaproid or "kb 101" or kb101 or lomoparan or lomoparin or mucoglucuronan or org 10172 or org10172 or orgaran).tw,kw.
30 danaproid.rn.
31 deligoparin*.tw,kw.
32 deligoparin.rn.
33 ((heparin adj1 dihydergot) or (dihydroergotamine adj1 heparin) or Embolex or (heparin

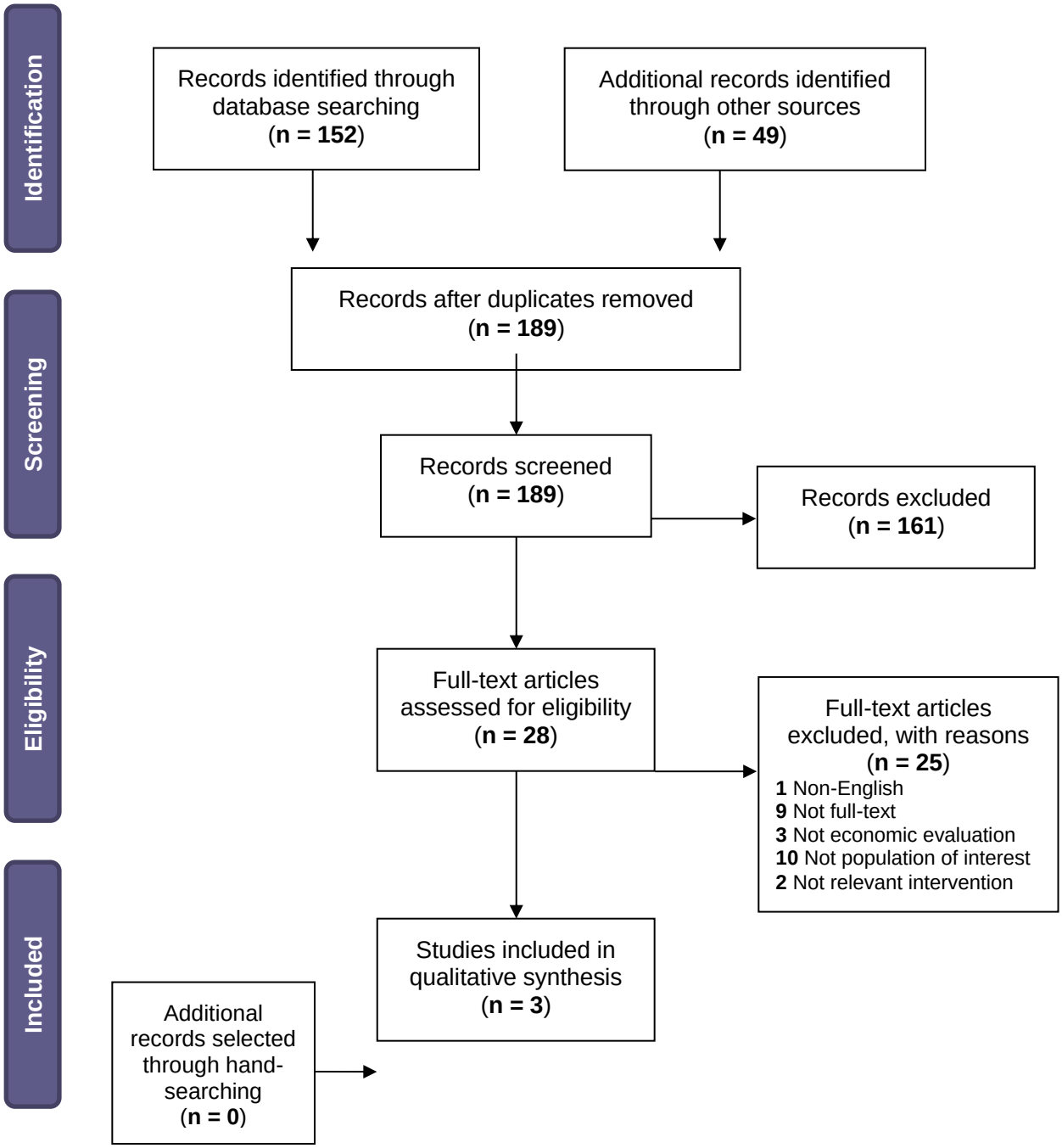
adj1 DHE)).tw,kw.
34 heparin-dihydergot.rn.
35 idrabiotaparinux.tw,kw.
36 idrabiotaparinux.rn.
37 idraparinux.tw,kw.
38 idraparinux.rn.
39 livaraparin calcium.tw,kw.
40 livaraparin calcium.rn.
41 minolteparin*.tw,kw.
42 minolteparin.rn.
43 rd 11885.tw,kw.
44 rd 11885.rn.
45 tafoxiparin*.tw,kw.
46 tafoxiparin.rn.
47 (fondaparinux or arixtra or quixidar or xantidar or "Org 31540" or "SR 90107" or "SR 90107A" or "UNII-X0Q6N9USOZ" or "UNII-J177FOW5JL").tw,kw.
48 (fondaparinux or fondaparinux sodium).rn.
49 or/1-48
50 Venous Thrombosis/
51 Upper Extremity Deep Vein Thrombosis/
52 (deep adj (venous or vein$1 or vena) adj2 thrombos*).tw,kw.
53 (("deep venous" or "deep vein") adj2 (thrombus or thrombophlebitis or "thrombo-phlebitis")).tw,kw.
54 (DVT or DVTs).tw,kw.
55 Venous Thromboembolism/
56 ((venous or vein$1 or vena) adj2 (thromboemboli* or thrombo-emboli*)).tw,kw.
57 (VTE or VTEs).tw,kw.
58 ((prevent* or prophyla* or chemoprophyla* or chemo-prophyla*) adj3 (thromboemboli* or thrombo-embolic* or thrombos#s or VTE or VTEs)).tw,kw.
59 (thromboprophyla* or thrombo-prophyla*).tw,kw.
60 or/50-59
61 Cancer*.tw,kw.
62 Neoplasm*.tw,kw.
63 Malignan*.tw,kw.
64 or/61-63
65 49 and 60 and 64
66 exp Animals/ not (exp Animals/ and Humans/)
67 65 not 66
68 67 use prmz
69 Economics/
70 exp "Costs and Cost Analysis"/
71 Value of Life/
72 exp Economics, Hospital/
73 Economics, Medical/
74 Economics, Nursing/
75 Economics, Pharmaceutical/
76 or/69-75

77 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
78 (expenditure$ not energy).ti,ab.
79 (value adj1 money).ti,ab.
80 budget$.ti,ab.
81 or/77-80
82 76 or 81
83 68 and 82
84 exp low molecular weight heparin/
85 LMWH.tw,kw.
86 ((low molecular weight or LMW) adj1 heparin).tw,kw.
87 (Dalteparin* or FR-860 or Fragmin or Fragmine or Kabi-2165 or "K 2165"' or K2165 or Tedelparin or low liquemin).tw,kw.
88 (Enoxaparin* or Clexan* or EMT-966 or EMT-967 or HSDB 7846 or Klexane or Lovenox or PK10169 or PK 10169 or "PK-10,169" or RP 54563 or UNII-8NZ41MIK1O).tw,kw.
89 679809-58-6.rn.
90 (nadroparin* or CY 216 or CY 216d or CY216 or CY216d or Fraxiparin* or LMF CY-216 or Nadroparin Calcium or Nadroparine or Nadrohep or Fraxodi or Seleparin* or Tedegliparin*).tw,kw.
91 (tinzaparin* or Innohep or UNII-7UQ7X4Y489).tw,kw.
92 (bemiparin* or hibor or phivor or ardeparin* or UNII-N3927D01PB).tw,kw.
93 (certoparin* or Alphaparin* or Alpha-parin* or Mono-Embolex or Monoembolex).tw,kw.
94 (Reviparin* or Clivarin* or LU 47311 or LU47311 or lomorin).tw,kw.
95 (parnaparin* or parvoparin* or fluxum or lohepa or lowhepa or minidalton or op 2123 or CB-01-05-MMX).tw,kw.
96 (semuloparin* or mulsevo or visamerin or AVE 5026 or AVE5026 or UNII-4QW4AN84NQ).tw,kw.
97 sevuparin*.tw,kw.
98 (ardeparin* or normifio or normiflo or rd heparin or wy 90493 or wy90493).tw,kw.
99 (adomiparin* or "m 118" or m118).tw,kw.
100 antixarin*.tw.
101 ("cy 222" or cy222).tw,kw.
102 (danaproid or "kb 101" or kb101 or lomoparan or lomoparin or mucoglucuronan or org 10172 or org10172 or orgaran).tw,kw.
103 308068-55-5.rn.
104 deligoparin*.tw,kw.
105 ((heparin adj1 dihydergot) or (dihydroergotamine adj1 heparin) or Embolex or (heparin adj1 DHE)).tw,kw.
106 idrabiotaparinux.tw,kw.
107 idraparinux.tw,kw.
108 162610-17-5.rn.
109 livaraparin calcium.tw,kw.
110 minolteparin*.tw,kw.
111 rd 11885.tw,kw.
112 tafoxiparin*.tw,kw.
113 (fondaparinux or arixtra or quixidar or xantidar or "Org 31540" or "SR 90107" or "SR 90107A" or "UNII-X0Q6N9USOZ" or "UNII-J177FOW5JL").tw,kw.

114 114870-03-0.rn.
115 or/84-114
116 deep vein thrombosis/
117 upper extremity deep vein thrombosis/ or lower extremity deep vein thrombosis/
118 (deep adj (venous or vein$1 or vena) adj2 thrombos*).tw,kw.
119 (("deep venous" or "deep vein") adj2 (thrombus or thrombophlebitis or "thrombo-phlebitis")).tw,kw.
120 (DVT or DVTs).tw,kw.
121 venous thromboembolism/
122 ((venous or vein$1 or vena) adj2 (thromboemboli* or thrombo-emboli*)).tw,kw.
123 (VTE or VTEs).tw,kw.
124 ((prevent* or prophyla* or chemoprophyla* or chemo-prophyla*) adj3 (thromboemboli* or thrombo-embolic* or thrombos#s or VTE or VTEs)).tw,kw.
125 (thromboprophyla* or thrombo-prophyla*).tw,kw.
126 or/116-125
127 Cancer*.tw,kw.
128 Neoplasm*.tw,kw.
129 Malignan*.tw,kw.
130 or/127-129
131 115 and 126 and 130
132 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
133 exp humans/ or exp human experimentation/ or exp human experiment/
134 132 not 133
135 131 not 134
136 135 use emez
137 health economics/
138 exp economic evaluation/
139 exp "health care cost"/
140 exp pharmacoeconomics/
141 or/137-140
142 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
143 (expenditure$ not energy).ti,ab.
144 (value adj2 money).ti,ab.
145 budget$.ti,ab.
146 or/142-145
147 141 and 146
148 136 and 147
149 83 or 148
150 limit 149 to yr="2000-Current"
151 remove duplicates from 150

Appendix A2: Results of Search

Exhibit 1: Flow diagram of the selection process for potentially relevant studies.



Appendix A3: List of Excluded Studies

Exhibit 2: List of excluded studies and reasons for exclusion

Study Reference	Reason for exclusion
Jara PL, Caballero EC, Elias HT, Ferrer GM, Marquez PS, Cayuela A, et al. Outpatient management of patients with deep vein thrombosis and cancer: a study of safety, cost and budget impact. Med Clin (Barc). 2012 Apr 7;138(8):327-31.	Non-English
Uppal S, Hernandez E, Dutta M, Dandolu V, Rose S, Hartenbach E. Prolonged postoperative venous thrombo-embolism prophylaxis is cost-effective in advanced ovarian cancer patients. Gynecologic Oncology. 2012;127(3):631-7.	Not population of interest
Powers A, Simons WR, Choe Y, Faria C. Real-world evaluation of the cost-effectiveness of prophylactic treatment in the prevention of recurrent venous thromboembolism in patients with cancer: Dalteparin versus enoxaparin [abstract]. Journal of Managed Care Pharmacy. 2011;17(3):268-9. (Presented at 23rd Annual Meeting and Showcase of the Academy of Managed Care Pharmacy in Minneapolis, MN United States; 27 Apr 2011 - 29 Apr 2011).	Not full text
Baser O, Sengupta N, Dysinger A, Wang L. Thromboembolism prophylaxis in medical inpatients: Effect on outcomes and costs. American Journal of Managed Care. 2012;18(6):294-302.	Not economic evaluation
Pishko AM, Smith KJ, Ragni MV. Anticoagulation in ambulatory cancer patients with no indication for prophylactic or therapeutic anticoagulation: A cost-effectiveness analysis from a U.S. perspective. Thrombosis and Haemostasis. 2012;108(2):303-10.	Not population of interest
Rossi A, Schackman B, Akhtar NH, Tagawa ST. Primary VTE prophylaxis in ambulatory cancer patients receiving chemotherapy-a cost analysis [abstract]. Thrombosis Research. 2012;129:S185-S186. (Presented at 6th International Conference on Thrombosis and Hemostasis Issues in Cancer in Bergamo, Italy; 20 Apr 2012 - 22 Apr 2012).	Not full text
Pishko A, Smith KJ, Ragni MV. Anticoagulation in ambulatory cancer patients [abstract]. Blood. 2011;118(21). (Presented at 53rd Annual Meeting of the American Society of Hematology, ASH 2011 in San Diego, CA United States; 10 Dec 2011 - 12 Dec 2011).	Not full text
Mucino-Ortega E, Gutierrez-Colin CI, Galindo-Suarez RM. Economic evaluation of antithrombotic therapies in patients with cancer in Mexico [abstract]. Value in Health. 2012;15(4):A221. (Presented at 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Washington, DC United States; 02 Jun 2012 - 06 Jun 2012).	Not full text

Study Reference	Reason for exclusion
Teoh D, Berchuck A, Secord AA, Lee PS, Lowery WJ, Sfakianos GP, et al. Cost comparison of strategies for the management of venous thromboembolic event risk following laparotomy for ovarian cancer. Gynecologic Oncology. 2011;122(3):467-72.	Not population of interest
Hitos K, Stratton C, Fletcher JP. Cost-effectiveness of pharmacological prophylaxis in preventing venous thromboembolism and associated long term complications in gynaecological oncology surgery [abstract]. Journal of Thrombosis and Haemostasis. 2011;9:903. (Presented at 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting in Kyoto, Japan; 23 Jul 2011 - 28 Jul 2011).	Not full text
Uppal S, Dandolu V, Hernandez E. Cost-effectiveness of extended postoperative venous thromboembolism prophylaxis in gynecologic pncology patients [abstract]. Gynecologic Oncology. 2011;120:S122. (Presented at 42nd Annual Meeting of the Society of Gynecologic Oncologists in Orlando, FL United States; 06 Mar 2011 - 09 Mar 2011).	Not full text
Bradley CT, Brasel KJ, Miller JJ, Pappas SG. Cost-effectiveness of prolonged thromboprophylaxis after cancer surgery. Annals of Surgical Oncology. 2010;17(1):31-9.	Not population of interest
Choe Y, Powers A, Simons W. A real world evaluation of the costs of prophylactic treatment in the prevention of recurrent venous thromboembolism in patients with cancer: Dalteparin versus warfarin [abstract]. Journal of Managed Care Pharmacy. 2010;16(7):515-6. (Presented at Professional Poster Presentations at AMCP's 2010 Educational Conference in St.Louis, MO United States; 13 Oct 2010 - 15 Oct 2010).	Not full text
De ME, Schluckebier L, Fernandes RA, Bernardina E, Levy RA, Quintella FF. A probabilistic cost-effectiveness analysis for deep-vein thrombosis prophylaxis enoxaparin versus no intervention in oncology patients following surgery in Brazil [abstract]. Journal of Thrombosis and Haemostasis. 2009;7(S2):482-3. (Presented at 22nd Congress of the International Society of Thrombosis and Haemostasis in Boston, MA United States; 11 Jul 2009 - 16 Jul 2011).	Not full text
Arreola-Ornelas H, Rosado-Buzzo AA, Garcia-Mollinedo MDL, Dorantes-Aguilar J, Mould-Quevedo J, vila-Loaiza G. A pharmacoeconomic analysis of prophylaxis therapies and treatment of venous thromboembolism (VTE) in Mexican patients with cancer [abstract]. Value in Health. 2009;12(3):A151. (Presented at ISPOR 14th Annual International Meeting in Orlando, FL United States; 16 May 2009 - 20 May 2009).	Not full text
Wade WE, Spruill WJ. Cost-effectiveness of dalteparin versus unfractionated heparin as venous thromboembolism prophylaxis	Not population of interest

Study Reference	Reason for exclusion
in malignant gynecologic surgery. American Journal of Therapeutics. 2008;15(6):512-5.	
Bullano MF, Willey V, Hauch O, Wygant G, Spyropoulos AC, Hoffman L. Longitudinal evaluation of health plan cost per venous thromboembolism or bleed event in patients with a prior venous thromboembolism event during hospitalization. Journal of managed care pharmacy : JMCP. 2005;11(8):663-73.	Not economic evaluation
Gozzard D, Hutchinson J, Lloyd A, Hutchings A. Economic evaluation of extended and conventional prophylaxis with enoxaparin against venous thromboembolism in patients undergoing surgery for abdominal cancer. Journal of Medical Economics. 2004;7(53-65):53-65.	Not population of interest
Dainty L, Maxwell GL, Clarke-Pearson DL, Myers ER. Cost-effectiveness of combination thromboembolism prophylaxis in gynecologic oncology surgery. Gynecologic Oncology. 2004;93(2):366-73.	Not population of interest
Chau Q, Cantor SB, Caramel E, Hicks M, Kurtin D, Grover T, et al. Cost-effectiveness of the bird's nest filter for preventing pulmonary embolism among patients with malignant brain tumors and deep venous thrombosis of the lower extremities. Supportive Care in Cancer. 2003;11(12):795-9.	Not relevant intervention
Maxwell GL, Myers ER, Clarke-Pearson DL. Cost-effectiveness of deep venous thrombosis prophylaxis in gynecologic oncology surgery. Obstetrics and Gynecology. 2000;95(2):206-14.	Not population of interest
Cirujeda JL, Granado PC. A study on the safety, efficacy, and efficiency of sulodexide compared with acenocoumarol in secondary prophylaxis in patients with deep venous thrombosis. Angiology. 2006;57(1):53-64.	Not economic evaluation
Santamaria A, Juarez S, Reche A, Gomez-Outes A, Martinez-Gonzalez J, Fontcuberta J. Low-molecular-weight heparin, bemiparin, in the outpatient treatment and secondary prophylaxis of venous thromboembolism in standard clinical practice: the ESFERA Study. Int J Clin Pract. 2006;60(5):518-25.	Not relevant intervention
Caro JJ, Getsios D, Caro I, O'Brien JA. Cost effectiveness of tinzaparin sodium versus unfractionated heparin in the treatment of proximal deep vein thrombosis. PharmacoEconomics. 2002;20(9):593-602.	Not population of interest
Johnston JA, Brill-Edwards P, Ginsberg JS, Pauker SG, Eckman MH. Cost-effectiveness of prophylactic low molecular weight heparin in pregnant women with a prior history of venous thromboembolism. Am J Med. 2005;118(5):503-14.	Not population of interest

Appendix A4: List of Included Studies

Exhibit 3: List of included studies within the review.

Reference #	Study Reference
14	Dranitsaris G, Vincent M, Crowther M. Dalteparin versus warfarin for the prevention of recurrent venous thromboembolic events in cancer patients: A pharmacoeconomic analysis. PharmacoEconomics. 2006;24(6):593-607.
1	Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for secondary prophylaxis of cancer-related venous thromboembolism. Thrombosis and Haemostasis. 2005;93(3):592-9.
15	Avritscher EBC, Cantor SB, Shih Y-C, Escalante CP, Rivera E, Elting LS. Cost-minimization analysis of low-molecular-weight heparin (dalteparin) compared to unfractionated heparin for inpatient treatment of cancer patients with deep venous thrombosis. Supportive Care in Cancer. 2004;12(7):531-6.

Appendix A5: Characteristics of Reviewed Studies

Exhibit 4: Brief overview of included studies.

First author, Year	Country	Sponsorship	Study type	Model type	Time horizon	Included interventions
Aujeski, 2005	United States	Independent	CEA/CUA	Decision tree	Lifetime	Dalteparin, warfarin
Avritscher, 2004	United States	Pharmacia	CMA	Decision tree	Duration of treatment (approx. 1 week)	Dalteparin, unfractionated heparin
Dranitsaris, 2006	Canada	Pfizer	CEA/CUA	Trial-based	Unclear	Dalteparin, warfarin

Note: CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis

Exhibit 5: Detailed characteristics of included studies.

First Author, Year	Aujesky, 2005	Avritscher, 2004	Dranitsaris, 2006
Sponsorship	Independent	Pharmacia	Pfizer
Country	United States	United States	Canada
Perspective	HCP and societal	HCP	HCP
Study type	CEA/CUA	CMA	CEA/CUA
Comparators	Dalteparin 200 IU/kg/day (month 1), 150 IU/kg/day (months 2-6), subcutaneous injection Warfarin (target international normalized ratio 2.5)	Dalteparin 2,500 IU syringe Unfractionated heparin (UFH): Heparin sodium 10 mg vial (1,000 U/mL) Warfarin sodium 2 mg tablet	Dalteparin, subcutaneous 200 IU/kg/day (month 1), 150 IU/kg/day (months 2-6) Warfarin (dose unspecified)
Target population	65 year old cancer patients who experienced a venous thromboembolic event (secondary prophylaxis of cancer-related VTE)	Inpatient cancer patients with acute DVT (initial management of DVT)	Cancer patients who experienced a venous thromboembolic event (secondary prophylaxis of cancer-related VTE)
Time horizon	Lifetime	Duration of treatment (approx.. 1 month)	Unclear
Type of model	Decision tree	Decision tree	Trial-based analysis
Adverse events	Not included	n/a	Included
Results	Dalteparin vs. warfarin: ICUR = $149,865/QALY Unadjusted ICER = $115,847/LY Dalteparin: LY=1.442 QALYs=1.097 Cost=$15,329 Warfarin: LY=1.377 QALYs=1.046 Cost=$7720 1.00 USD = 1.59 CAD; 2002	Daltparin: Mean cost of inpatient care = $3383 (95% CI $2683, $4083) UFH: Mean cost of inpatient care = $4952 (95% CI $4718, $5185) 1.00 USD = 1.58 CAD; 2003	Dalteparin vs oral therapy (warfarin): Cost per VTE avoided = $27,700 Cost per QALY gained = $13,751

Appendix B – De novo Economic Evaluation

Research Question

RQ2. Based on a de novo economic model, what is the comparative cost-effectiveness of LMWH, as compared with warfarin for the **prevention** of recurrent DVT or PE in patients with cancer?

Study Objectives

Based on the research question, the objective of the study was to address the following specific question:

- What is the cost effectiveness of prophylactic therapy with LMWH as compared with warfarin for the prevention of recurrent VTE in patients with cancer?

Background

Current guidelines recommend that, for cancer patients with established VTE, LMWH be the initial anticoagulant treatment used for a period of 5 to 10 days.[18] They also recommend that LMWH be given for at least 6 months as the preferred approach to long-term anticoagulant therapy. These recommendations are based on the comparative effectiveness of LMWH versus vitamin K antagonists in preventing recurrent VTE.

A recent Cochrane review addressed the question of the comparative effectiveness of LMWH versus oral anticoagulants in the long term secondary prophylaxis of venous thromboembolism in patients with cancer.[2] Seven RCTs were included within the meta-analysis. Data were available regarding the impact of treatments on mortality, recurrent VTE, major bleeding and minor bleeding. The trials often differed with respect to the original treatment for the VTE; in some cases, UFH or LMWH was used alone, , while in some studies a combination of treatments were used (either UFH or warfarin with LMWH) The authors concluded that long term treatment with LMWH reduced the rate of recurrent venous thromboembolism as compared with vitamin K antagonists, but there was no significant difference between the treatments with respect to mortality. There was also no evidence of a differential effect with respect to either major or minor bleeding. Based on this evidence, LMWH medications have a beneficial effect with respect to the prevention of recurrent VTE in cancer patients; however, they do not improve survival in this population. The cost of treatment with LMWH compared with warfarin is considerably higher; therefore, in deciding to recommend use of LMWH for long term prophylaxis in these patients, consideration must be given to the cost implications.

Given the conflicting findings of two previous studies examining the comparative cost effectiveness of LMWH and warfarin in the prevention of recurrent VTE in cancer patients (see Appendix A),[1,14] conducting a more robust cost effectiveness analysis from a Canadian perspective based on the CLOT trial would be informative.[17] The recent Cochrane review also

provided estimates of the relative effect of LMWH versus vitamin K antagonists derived from a meta-analysis of studies. Estimation of the comparative cost effectiveness of LMWH versus vitamin K antagonists based on the results of this meta-analysis will also provide better insight into the recommended treatment protocol.

Economic Evaluation

To address the research question, a de novo economic decision analytic model was developed to examine the cost effectiveness of LMWH versus warfarin. The model was adapted to allow incorporation of effectiveness data from two different sources. In the first analysis (Decision Analytic Model 1), the estimated effectiveness of LMWH was derived from the CLOT trial, whereas, in the second analysis (Decision Analytic Model 2), it was sourced from the Cochrane meta-analysis.[2,17]

Although a Markov model for this analysis was originally explored, the difference in treatments is limited to an impact on recurrence of VTE and there is no evidence of a differential impact on mortality. There is therefore no reason to suspect that the long term costs or benefits of treatment would differ between the two treatment groups. A decision tree model is therefore more suitable for addressing the decision problem.

In the base case, the analysis time frame for the two models was limited to the duration of follow up within the CLOT clinical trial in which patients were treated for 6 months. Sensitivity analyses were conducted extending the analysis time frame to 12 months, with treatment remaining fixed at 6 months.

The decision analytic model was based on the model developed by Aujesky et al. (2005) and modified for the Canadian setting to incorporate alternate effectiveness data and treatment duration information.[1] The analysis is based on a cohort of 65 year old patients with a diagnosis of cancer, who have experienced a venous thromboembolic event. This is consistent with previous models and based on the mean age of patients in studies of cancer-related VTE.

In both analyses, the costs and quality adjusted life years (QALYs) associated with LMWH compared with warfarin in the prevention of recurrent VTE in cancer patients were estimated. Analysis was conducted from the perspective of the Ontario healthcare system.

Clinical Parameters

As per the CLOT trial, the cohort of patients within the LMWH arm received dalteparin at a dose of 200 IU per kilogram once daily for the first month, reduced to 150 IU per kilogram daily for months 2 to 6.[17] The warfarin cohort also received LMWH (dalteparin) for 6 days at a dose of 200 IU per kilogram concurrent with warfarin at a dose titrated to a target INR of 2.5 which was continued for the 6-month treatment period. The dose of warfarin was 5 mg per day and the dose of dalteparin was estimated based on a weight of 70 kg. The duration of LMWH administration within the warfarin cohort was tested within sensitivity analyses as the recommended duration varies from 5 to 10 days.

At any time during follow-up, patients were at risk of experiencing a recurrent VTE event. Within Decision Analytic Model 1, the probability of recurrent VTEs for both LMWH and

warfarin was derived from the CLOT trial. Within Decision Analytic Model 2, the probability of recurrent VTE for warfarin was sourced from the CLOT clinical trial and the relative risk of recurrent VTE with LMWH versus warfarin sourced from the Cochrane meta-analysis was applied to derive the probabilities for LMWH. Within the CLOT trial, the number of VTE events that were DVTs and the number that were PEs were reported and these probabilities were used within the first analysis. This detail was not available from the Cochrane meta-analysis. Within the base case analysis for Decision Analytic Model 2, we assumed the same total breakdown in DVTs versus PEs as was found with LMWH and warfarin combined within the CLOT trial. This was tested within sensitivity analyses.

Patients on both therapies were also at risk of hemorrhagic events, specifically major bleeds, both intracranial and non-intracranial, and minor bleeds. The probability of these events was sourced from the CLOT clinical trial for each treatment within Decision Analytic Model 1. Within Decision Analytic Model 2, the probability of major and minor bleeds with warfarin was sourced from the CLOT clinical trial, with relative risk of these events for LMWH versus warfarin from the Cochrane review applied to the warfarin events to estimate the probability with LMWH. It is difficult to establish accurate estimates of the risk of intracranial hemorrhage (ICH) from individual clinical trials; therefore, we took the same approach as Aujesky et al. (2005) and used an estimate of the probability that a major bleed is an ICH from a large meta-analysis.[19] Patients experiencing an ICH were assumed to discontinue therapy.

Patients were also at risk of dying from both recurrent VTE events and from other causes. The probability of death was derived from the CLOT clinical trial for Decision Analytic Model 1; the previously described approach of applying the relative risk from the Cochrane meta-analysis to the warfarin probability from the CLOT trial was used for estimating the risk of mortality in Decision Analytic Model 2. There were no significant differences in mortality between treatments in any of the clinical trials; however, the current analysis incorporated the survival estimates from the original trial and meta-analysis, thereby reflecting a slight benefit with LMWHs versus warfarin with respect to survival.

Model Structure

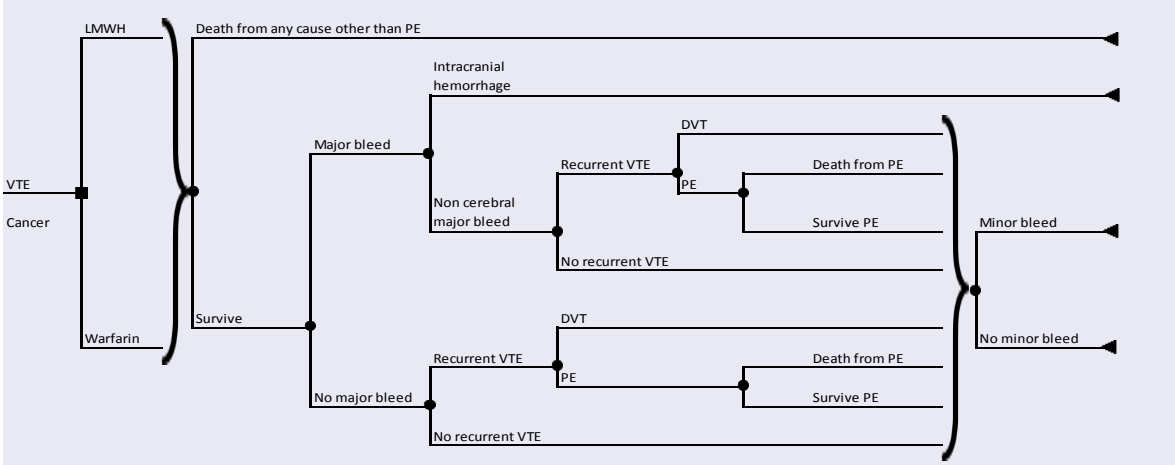
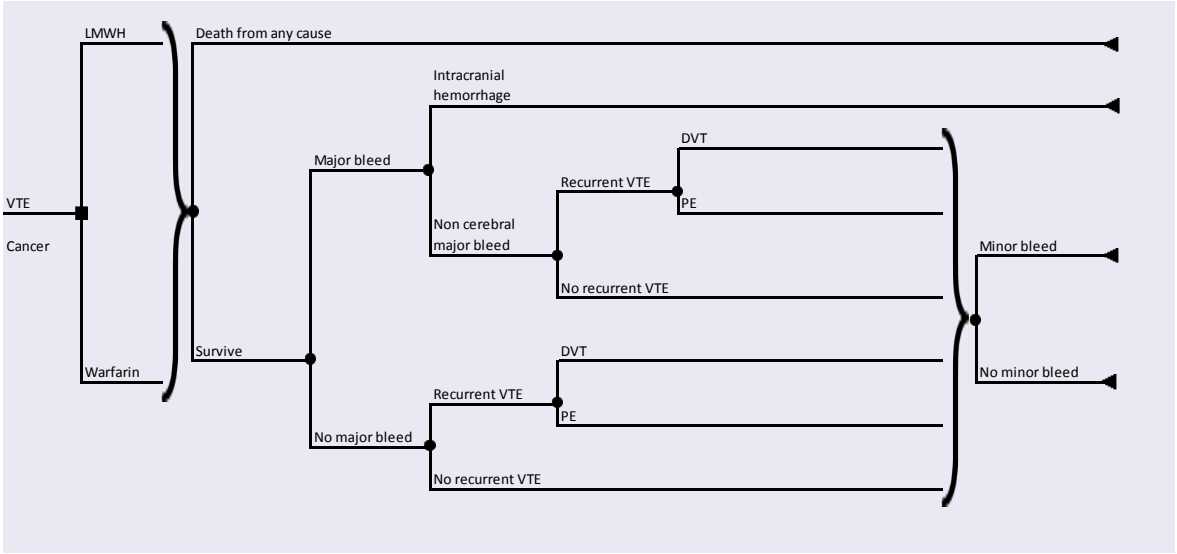


Exhibit 6: Schematic of Decision Analytic Model 1

Exhibit 7: Schematic of Decision Analytic Model 2



Data Inputs

Data used within the economic model are provided in Appendix B1: Data Estimates. Details of data sources are provided below.

Utilities

The utilities associated with each disease state were derived from the literature. As all patients within the study had a diagnosis of cancer, an average utility value associated with the diagnosis of cancer of 0.73 was applied to patients who experienced no subsequent events throughout the follow-up period.[11] This estimate was derived from a large population sample using the Health Utilities Index.

The disutility of events experienced by patients during the follow-up period would therefore result in a utility value below 0.73. As thromboembolic events, adverse bleeding events and potentially drug therapy may result in reduced utility, and given that patients may experience more than one event, consideration must be given to the interaction between the disutility associated with these events. Both an additive and a multiplicative approach were taken to estimate the combined impact of multiple events. The additive approach was adopted for the base case analysis.

Most of the events within the clinical trials are temporary and therefore both the magnitude of the impact on utility and the duration of the effect must be taken into account. The utility values for DVT, PE, major bleed, and minor bleed were sourced from a study which used a time trade off method for eliciting utilities in patients who had previously experienced a VTE.[12] The utility values were adjusted to reflect the duration of the event. In the base case, DVT, PE, and major bleed were assumed to persist for the average length hospitalization plus 2 additional days. This was tested within sensitivity analyses. Minor bleed was assumed to last only 1 day.

Intracranial hemorrhage, on the other hand, results in a permanent disutility. The utility value for ICH was also derived using the time trade off method.[13] This study estimated the utility value for ICH as 0.6, which is consistent with other references.[20]

Some other studies have included a disutility for patients taking warfarin but not for those taking LMWH. The rationale provided for this disutility is generally attributed to the need for INR monitoring with warfarin. LMWH, however, requires daily injections which may also impact some patients' quality of life. Within the base case analysis, treatment with either warfarin or LMWH was assumed to result in no reduction in quality of life. This assumption was tested within sensitivity analysis by assigning a disutility to warfarin.

Resource Use and Costs

Acute Events

Within the models, treatment of DVT was consistent with the approach taken within the CLOT clinical trial in which LMWH was used for acute DVTs regardless of the prophylactic therapy. In the base case we assumed 20% of DVTs were treated within the hospital and 80% as outpatients.[21] The percentage treated within hospital was varied from 0% to 50% in sensitivity analyses.

The cost of treating DVTs and PEs in hospital was sourced from an Ontario administrative database which provides the average costs per patient including all hospital care except physician visits and provides the average length of stay by diagnosis.[3] We assumed one physician visit per day in hospital with the physician costs sourced from the MOHLTC physician fee reference.[4]

The cost of outpatient treatment of DVTs was sourced from a Canadian costing study.[5] The estimated cost included laboratory tests, nursing activities and medical imaging procedures. To this estimate, we added the cost for an initial physician visit and a follow up visit at 5 to 7 days after initiation of LMWH, as occurred within the study. We also added the cost of treatment with LMWH.

The cost of hospital treatment for a major bleed was also sourced from an Ontario administrative database which provides both the average length of stay and the average costs per patient including all hospital care except physician visits.[3] The diagnostic category of gastrointestinal hemorrhage was used as a proxy for major bleed. To this we added the cost of one physician visit per day in hospital. This resulted in a cost of $4882 per case, which is comparable to the value within other published references; for example, $4743 per episode in a cost-effectiveness study of dabigatran.[22]

The cost of treating a minor bleed was assumed to include the cost of a physician visit, a complete blood cell test, and an INR test for those receiving warfarin.

The cost of intracranial hemorrhage included both the acute management cost and the continued follow-up costs. The event was assumed to occur, on average, at the mid-point of the treatment interval, and therefore the follow-up costs were for one half of the duration of the model. These costs were sourced from a Canadian costing study which prospectively estimated the one year follow-up costs of stroke based on type of stroke.[6] The follow-up costs

for hemorrhagic stroke were adjusted to relate to the time horizon of the model.

Prophylactic Treatment

The costs associated with the preventative therapies, LMWH and warfarin, were also included. Patients were assumed to receive prophylactic therapy for 6 months, as per the CLOT clinical trial protocol.[17] This assumption was tested within sensitivity analyses, by reducing the duration of treatment to the actual duration of therapy of the patients within the CLOT trial.[14]

The costs of the medications were sourced from the Ontario Drug Benefit Formulary.[7] The standard dispensing fee of $8.83 and a mark of up 8% were incorporated.

It is assumed that a portion of people receiving LMWH would require nursing assistance for administration. In the base case analysis this was estimated as 20% of patients and varied between 0% and 50% in sensitivity analyses.[1] A standard cost of a one-hour nurse homecare visit was included for these patients.[8]

Patients receiving warfarin require regular monitoring of their INR. In the base case analysis, it was assumed that INR would be monitored every 2 weeks. Increased and reduced frequencies were tested within sensitivity analyses.

Follow-up and Monitoring

The costs of physician follow-up and routine laboratory tests were also incorporated. Patients were assumed to visit their family physician for follow-up with the same frequency as reported within the CLOT clinical trial. The standard cost of a reassessment visit was sourced from the MOHLTC physician fee reference.[4]

Patients were also assumed to have regular laboratory monitoring including complete blood count (CBC), creatinine and liver function tests. The cost of these tests was sourced from the Ontario Laboratory Fee schedule.[9]

Cost Effectiveness

For the cost-utility analyses, costs and effects as measured by quality-adjusted life years gained associated with prophylactic treatment with LMWHs versus warfarin were estimated via the model. Discounting of costs and QALYs was not necessary.[23] Both a deterministic and a probabilistic sensitivity analysis were conducted.

Deterministic Sensitivity Analyses

Within the deterministic sensitivity analysis, alternative assumptions regarding parameter estimates and model structure were incorporated within the model and the impact on the cost-effectiveness ratio is reported. The analyses conducted are listed in Exhibit 8.

In extending the timeframe for the analysis to 12 months and a lifetime, a number of assumptions were required. Preliminary follow-up from the CLOT clinical trial indicated that the survival at 12 months with LMWH was 44% versus 42% with warfarin. These values were used to model survival from 6 months to 12 months. From 12 months onward, the same mortality rate was assumed for both therapies. Those with a history of ICH were assumed to

have a 25% higher rate of mortality. The long term follow-up costs for patients with a history of ICH and for patients with a history of VTE were also incorporated within these analyses. The monthly follow up cost for ICH is $3,716 and for VTE it was estimated at $57.[6,24]

Exhibit 8: Deterministic Sensitivity Analyses

Assumption	Base Case	Alternative Scenarios
Duration of LMWH for treatment of VTE within the warfarin cohort	6 days	5 to 10 days
Percentage of DVTs treated in hospital	20% in hospital and 80% as outpatients	0% in hospital and 50% in hospital
Total costs	Estimated via the model	Incorporating total costs from Dranisitaris et al.[14] cost effectiveness analysis inflated to 2015
Timeframe	6 month horizon	12 month horizon Lifetime horizon
Duration of treatment	Treatment for 6 months	Duration as per Dranisitaris et al.[14] (actual average duration of therapy within the CLOT tria)l-
Model 2: Duration of treatment	Treatment for 6 months	Treatment for 3 months
Model 2: VTEs that are DVTs versus PEs	As per the overall proportions for LMWH and warfarin combined within the CLOT trial	100% of VTEs being DVTs alone 50% of VTEs being DVTs alone
Utility Interaction	Additive model	Multiplicative model
Duration of disutility associated with acute event	Duration of hospitalization plus 2 days	Duration of hospitalization Duration of hospitalization plus 7 days
Utility values associated with acute events	Derived from literature	Assuming zero utility for duration of hospitalization for event
Disutility associated with drug therapy	No disutility associated with warfarin or LMWH therapy	A disutility of 0.03 per annum associated with warfarin
Percentage of patients requiring nursing assistance for LMWH administration	20%	0% and 50%

Frequency of INR monitoring with warfarin	Every 2 weeks	Weekly and every 4 weeks

Probabilistic Sensitivity Analyses

A probabilistic sensitivity analysis was conducted in order to estimate the impact of parameter uncertainty on the cost-effectiveness ratio. The parameters included within the PSA and their corresponding distributions are reported in Appendix B1: Data Estimates (Exhibit 19, Exhibit 20, and Exhibit 21). A gamma distribution was used for the duration of acute events, hospital length of stay and costs. A beta distribution was used for the probability of recurrent VTE (DVT or PE), the probability of bleeding (intracranial, major but non intracranial and minor) and the probability of death. Beta or gamma distributions were used for utility values and disutilities. In cases where the uncertainty around the parameter is not known, a standard error of 10% of the mean was estimated.

The results of the PSA are presented through a scatterplot of the incremental costs versus the incremental QALYs and by a cost-effectiveness acceptability curve depicting the probability that each treatment option is the most cost-effective at a range of threshold values for a QALY.

Findings

Base Case

Decision Analytic Model 1

The average cost of prophylactic treatment with LMWH was significantly higher at $8,537 per patient compared with warfarin at $3,030 per patient. The majority of the difference arises from the cost of the drug therapy. The daily cost of LMWH ranges between $29 and $35; whereas the daily cost of warfarin is only $0.22. Additionally, assuming a percentage of patients (20% in the base case) receiving LMWH require nursing assistance with administration results in greater drug-related costs with LMWH as compared with warfarin ($1,748 versus $322 per patient, respectively). The costs of acute events are slightly lower with LMWH, as would be expected given the reduction in recurrent VTEs; however, there were more major bleeds with dalteparin than with warfarin, which attenuates the difference between the two therapies with respect to acute event costs. (

Exhibit 9)

Exhibit 9: Comparison of costs between LMWH and warfarin in Decision Analytic Model 1

	LMWH	Warfarin
Drug costs	$4,171	$32
Drug related costs (physician visits, anticoagulant monitoring, labs, home nursing visits)	$1,748	$322
Event costs	$2,617	$2,676
Total costs	$8,537	$3,030

LMWH was more effective producing slightly greater QALYs than warfarin; specifically, LMWH produced 0.293 QALYs over the 6 months as compared with 0.291 with warfarin, a difference of 0.002 QALYs.

This resulted in an ICER of $1,692,395 per QALY for LMWH compared with warfarin. (Exhibit 10)

Exhibit 10: Comparative cost effectiveness of LMWH versus warfarin in Decision Analytic Model 1

	LMWH	Warfarin
Total costs	$8,537	$3,030
Total QALYs	0.293	0.291
ICER versus warfarin	$1,692,395 per QALY	

Decision Analytic Model 2

The results of Decision Analytic Model 2 incorporating the relative risk of events for LMWH from the Cochrane meta-analysis were consistent with those of Decision Analytic Model 1. The average cost of prophylactic treatment with LMWH was significantly higher at $8,371 per patient compared with warfarin at $3,074 per patient. Additionally, drug related costs for physician visits, laboratory monitoring and home nursing were higher with LMWH as compared with warfarin ($1,748 versus $322 per patient). The difference in the cost of acute events was greater with this model, with LMWH costs being $268 lower than with warfarin.

This is due to the fact that the difference in the probability of major bleeds with LMWH versus warfarin within the Cochrane review is lower than within the CLOT trial. (Exhibit 11)

Exhibit 11: Comparison of costs between LMWH and warfarin in Decision Analytic Model 2

	LMWH	Warfarin
Drug costs	$4,171	$32
Drug related costs (physician visits, anticoagulant monitoring, labs, home nursing visits)	$1,748	$322
Event costs	$2,452	$2,721
Total costs	$8,371	$3,074

LMWH was more effective and produced greater QALYs than warfarin with LMWH producing 0.293 QALYs over the 6 months as compared with 0.290 with warfarin, a difference of 0.003 QALYs.

This resulted in an ICER of $1,632,751 per QALY for LMWH compared with warfarin. (Exhibit 12)

Exhibit 12: Comparative cost effectiveness of LMWH versus warfarin in Decision Analytic Model 2

	LMWH	Warfarin
Total costs	$8,371	$3,074
Total QALYs	0.293	0.290
ICER versus warfarin	$1,632,751 per QALY	

Deterministic Sensitivity Analysis

Deterministic sensitivity analyses found the results to be robust to the incorporation of alternative estimates for costs, utilities, resource use, and model structure.

A threshold analysis was also conducted to determine the percentage reduction in the price of LMWH required for it to be considered cost effective at a willingness to pay per QALY value of $50,000 and $100,000. The analysis also assumed no administration costs for LMWH. Within decision analytic model 1, a price reduction of 87% was required at a WTP of $100,000 per QALY and a reduction of 91% was required at a WTP of $50,000 per QALY. Within decision analytic model 2, a price reduction of 82% was required at a WTP of $100,000 per QALY and a reduction of 86% was required at a WTP of $50,000 per QALY.

Exhibit 13: Deterministic sensitivity analysis results for Decision Analytic Model 1

Base Case Assumption	Alternate Assumption	ICER (cost per QALY) for LMWH vs warfarin
LMWH administered for 6 days for treatment of acute VTE in warfarin cohort	LMWH administered for 5 days LMWH administered for 10 days	$1,704,255 $1,644,959
Percentage of DVTs treated in hospital	0% treated in hospital 50% treated in hospital	$1,717,966 $1,654,040
Total costs of treatment estimated via model	Incorporation of Dranisitaris costs	$783,002
Timeframe of 6 months	Timeframe of 12 months Lifetime	$516,947 $175,903
Additive model for utility interaction	Multiplicative model for utility interaction	$1,692,537
Duration of disutility equal to length of hospital stay plus 2 days	Length of stay Length of stay plus 7 days	$1,706,365 $1,658,452
Utility values for acute events derived from literature	Utility values for acute events assumed to be zero for duration of hospital stay	$1,295,799
No disutility with warfarin therapy	Disutility of 0.03 per annum with warfarin therapy	$447,130
20% of patients on LMWH require nursing assistance	0% require nursing assistance 50% require nursing assistance	$1,219,378 $2,401,921
No disutility with warfarin therapy and 20% of patients on LMWH require nursing assistance	Disutility of 0.03 per annum with warfarin therapy and 0% require nursing assistance	$322,159
Frequency of INR monitoring every 2 weeks	Weekly frequency Monthly frequency	$1,674,193 $1,701,497

Exhibit 14: Deterministic sensitivity analysis results for Decision Analytic Model 2

Base Case Assumption	Alternate Assumption	ICER for LMWH vs warfarin
LMWH administered for 6 days for treatment of acute VTE in warfarin cohort	LMWH administered for 5 days LMWH administered for 10 days	$1,644,489 $1,585,799
Percentage of DVTs treated in hospital	0% treated in hospital 50% treated in hospital	$1,651,559 $1,604,539

Base Case Assumption	Alternate Assumption	ICER for LMWH vs warfarin
Total costs of treatment estimated via model	Incorporation of Dranisitaris costs	$785,313
Additive model for utility interaction	Multiplicative model for utility interaction	$1,727,424
Duration of disutility equal to length of hospital stay plus 2 days	Length of stay Length of stay plus 7 days	$1,672,621 $1,540,925
Utility values for acute events derived from literature	Utility values for acute events assumed to be zero for duration of hospital stay	$1,277,267
No disutility with warfarin therapy	Disutility of 0.03 per annum with warfarin therapy	$435,974
20% of patients on LMWH require nursing assistance	0% require nursing assistance 50% require nursing assistance	$1,158,365 $2,344,330
No disutility with warfarin therapy and 20% of patients on LMWH require nursing assistance	Disutility of 0.03 per annum with warfarin therapy and 0% require nursing assistance	$309,305
Frequency of INR monitoring every 2 weeks	Weekly frequency Monthly frequency	$1,614,494 $1,641,879
64% of VTEs are DVTs alone and 36% are PEs as per the distribution in the CLOT trial	0% of VTEs are PEs and 100% are DVTs 50% of VTEs are PEs and 50% are DVTs	$1,740,053 $1,594,162

Probabilistic Sensitivity Analysis

The results of the probabilistic sensitivity analysis for both models are presented below.

With respect to LMWH as compared with warfarin, LMWH was more effective in 67% and 71% of replications in Decision Analytic Model 1 and Decision Analytic Model 2, respectively, but more costly in 100% of replications in both models. (see Exhibit 15, Exhibit 17) As illustrated within the cost effectiveness acceptability curves, at a willingness to pay of either $50,000 or $100,000 per QALY there is a 0% chance that LMWH is more cost effective than warfarin. (see

Exhibit 16,

Exhibit 18)

Decision Analytic Model 1

Exhibit 15: Incremental Cost Effectiveness Plane for LMWH versus Warfarin (Model 1)

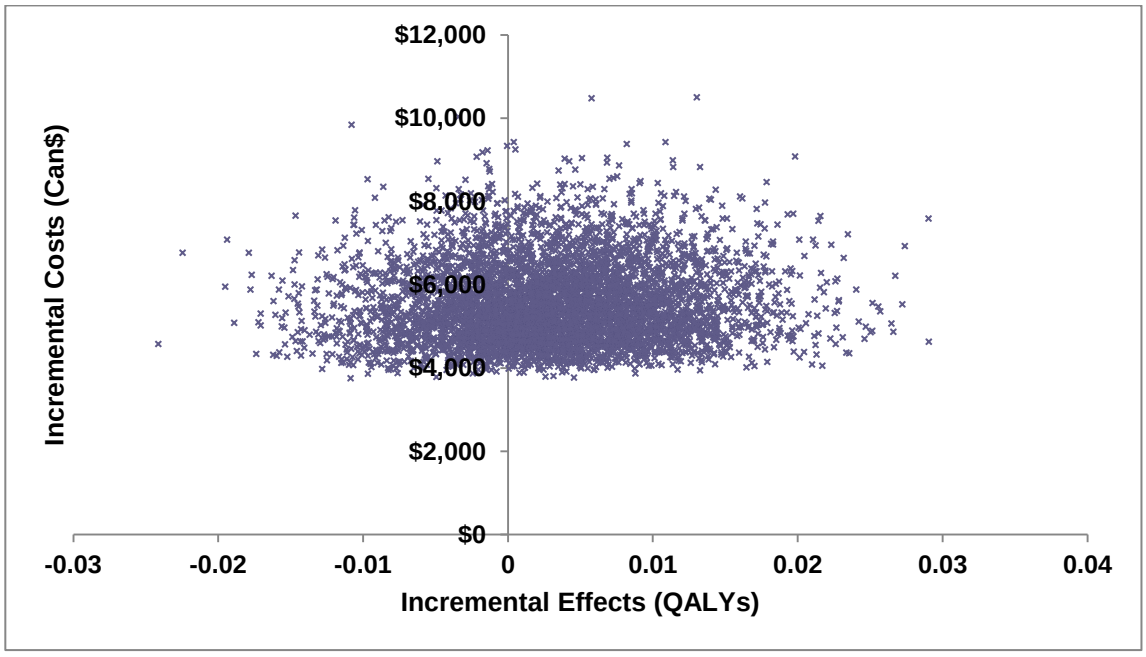
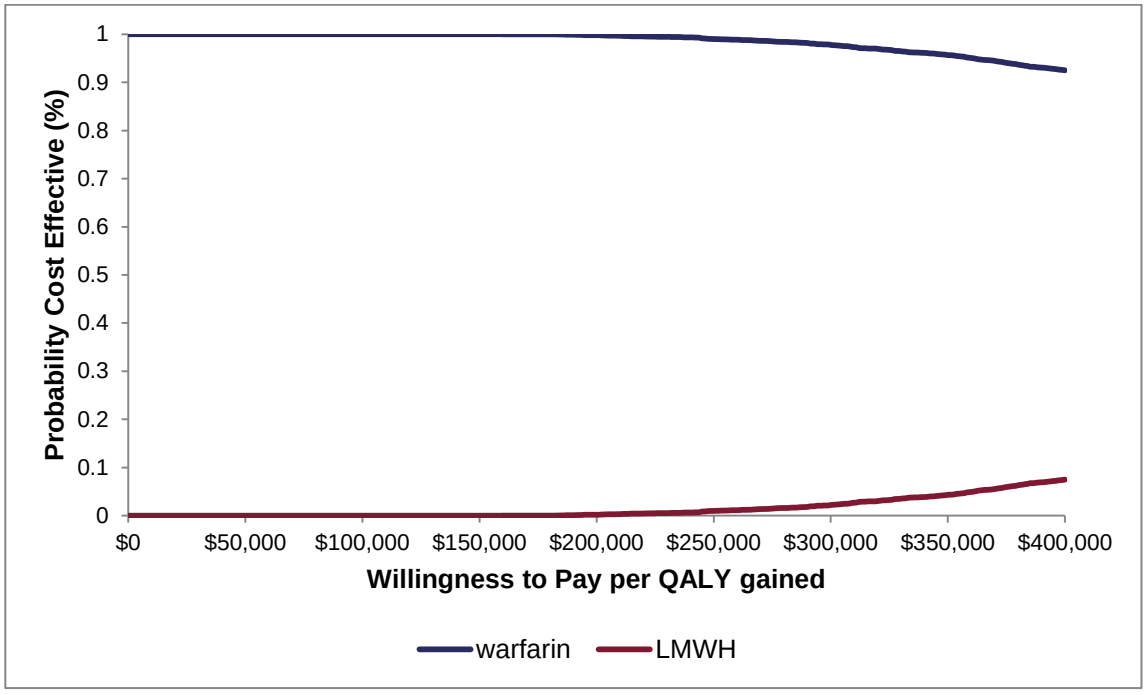


Exhibit 16: Cost Effectiveness Acceptability Curve (Model 1)



Decision Analytic Model 2

Exhibit 17: Incremental Cost Effectiveness Plane for LMWH versus Warfarin (Model 2)

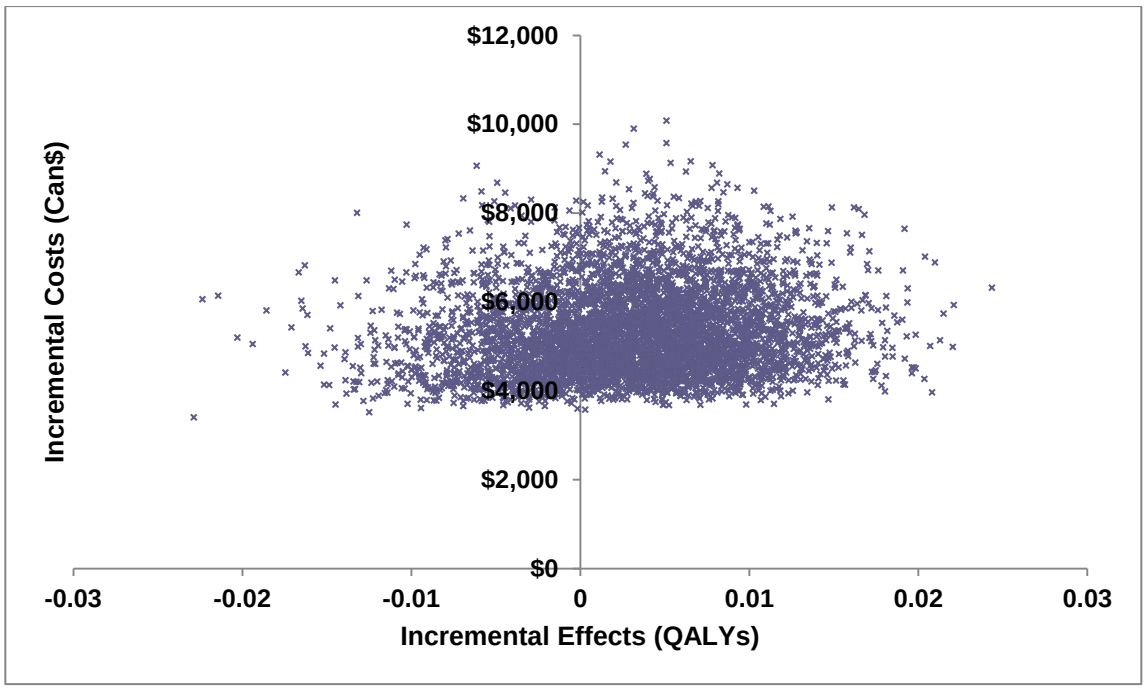
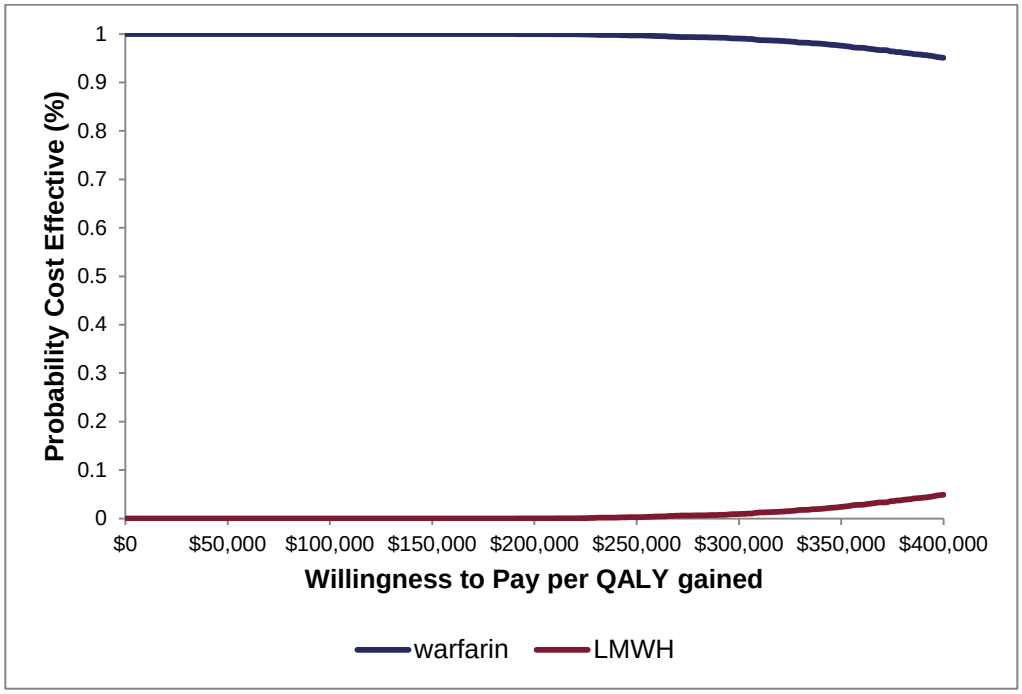


Exhibit 18: Cost Effectiveness Acceptability Curve (Model 2)



Overall Summary

In comparing the cost effectiveness of LMWH versus warfarin as long term prophylactic therapy against recurrent VTE LMWH results in slightly greater QALYs but is considerably more costly. The incremental cost effectiveness ratio for LWMH versus warfarin exceeds $1,000,000 per QALY. In clinical trials, LMWHs have been shown to decrease the rate of recurrent VTE; however, they have not been shown to improve survival and therefore the benefits relative to warfarin are small.

The study by Aujesky et al. (2005) found an ICER of US$149,865 per QALY for prophylactic treatment with LMWH as compared with warfarin.[1] The results of this analysis are not inconsistent with those of Aujesky et al. with respect to the comparative costs of prophylaxis with LMWH versus warfarin provided the difference in analytical perspective are taken into account; however, the estimate of the relative QALY gain with treatment was greater within the Aujesky et al. study. The majority of the benefit with LMWH treatment was due to an assumed survival gain with LMWHs. Neither the CLOT trial, nor the Cochrane meta-analysis found any evidence of improved survival with LMWH as compared with warfarin. Given that there is no evidence of a long term impact on survival, we limited the estimate of the mortality difference within the current study to what was reported within the randomized clinical trial and the Cochrane meta-analysis. At six months, 129 of 336 (38.39%) patients died within the warfarin treatment arm versus 125 of 336 (37.20%) patients within the LMWH arm. The relative risk of death with LMWH reported within the Cochrane meta-analysis was 0.96 (95% CI 0.81 – 1.13).[2] As the reduction in DVTs associated with LMWH produces only a small benefit in quality of life of patients, this leads to only a small difference in QALYs between treatments with significantly greater costs associated with LMWHs. Incorporating similar assumptions regarding differential survival between treatments over a lifetime horizon resulted in an ICER for LMWHs versus warfarin of $175,903 which is comparable to that

found by Aujesky et al.

The results of this analysis differ significantly from those of the previous cost-effectiveness analysis by Dranisitaris et al. (2006).[14] Although there was a difference in cost estimates based on the current economics modelling as compared with this previously published study, which is partially due to the exclusion of nursing costs from the previous study, the main differences between the studies arises is in the estimated QALY gain with LMWH versus warfarin. In the previous study, healthcare professionals were asked to provide a utility value for six months of treatment on warfarin compared with LMWH. Prior to valuing the health states, they were given a description of the treatment protocol and the results of the CLOT trial with respect to the reduction in DVTs with LMWH and no significant difference in impact of treatments on minor or major bleeds. With respect to mortality, they were provided with information from a post-hoc analysis of the CLOT trial that compared survival in a subset of patients with solid tumors. In patients with non-metastatic solid tumors, survival was greater with dalteparin than with warfarin; whereas, there was no difference in survival between treatments in those with metastatic solid tumors. This presentation of survival is misleading, as there was no survival benefit within the CLOT trial and it therefore holds that if there is a subset of patients whose survival was improved, there must also be a subset of patients in whom survival worsened. Additionally, the effectiveness data is not specific to the post hoc subset. This non-validated process of utility value elicitation resulted in unusually low utility values with an unusually large difference between treatments (0.66 for dalteparin versus 0.34 for warfarin). This utility difference was assumed to persist through the 6 months of treatment thereby resulting in a QALY gain with LMWH estimated at 0.157 as compared with 0.002 found within the current study.

Conclusions

In patients with cancer diagnosed with a VTE, long term prophylaxis with LMWH was not cost effective as compared with warfarin prophylaxis. The ICER for LMWH versus warfarin was greater than 1 million dollars per QALY gained. Even assuming no nursing administration costs for LMWH, a price reduction of greater than 80% would be required for LMWH to be considered cost effective at a willingness to pay threshold of $100,000 per QALY and a reduction of over 85% would be required at a willingness to pay threshold of $50,000 per QALY.

Appendix B1: Data Estimates

Exhibit 19: Data Estimates Used in both Decision Analytic Model 1 and 2

Input	Value (SE/95% CI/IQR)	Distribution	Source
Utility Values for Diseases			
Persistent Conditions			
Cancer	0.73 (0.10)	Beta	[11]
Intracranial hemorrhage	0.60 (0.25)	Beta	[13]
Acute Events			
DVT	0.84 (IQR: 0.64-0.98)	Gamma	[12]
Pulmonary embolism	0.63 (IQR: 0.36-0.86)	Gamma	[12]
Major bleed	0.65 (IQR: 0.49-0.86)	Gamma	[12]
Minor bleed	0.76 (IQR: 0.59-0.95)	Gamma	[12]
Duration of Acute Event (days)			
DVT	7.70 (SE: 0.77)^	Gamma	[3]
Pulmonary embolism	7.54 (SE: 0.75)^	Gamma	[3]
Major bleed	5.71 (SE: 0.57)^	Gamma	[3]
Minor bleed	1		Assumption
Resource Usage			
Physician visits while hospitalized	One physician visit for each day of hospitalization	Fixed	Assumption
Duration of treatment with LMWH for DVT	6 days (SE: 0.6)^	Gamma	[18]
Proportion of DVTs treated in hospital	20%	Beta (2, 8)~	Estimate
Nurse visits	20% of patients receiving LMWH	Beta (2, 8)~	Estimate
Hospital length of stay			
DVT	5.7 (SE: 0.57)^	Gamma	[3]
PE	5.5 (SE: 0.55)^	Gamma	[3]
Major bleed	3.7 (SE: 0.37)^	Gamma	[3]
Number of INR tests for patients receiving warfarin	12 (SE: 0.6)[#]	Gamma	[17]
Number of physician follow up visits	4 (SE: 0.4)^	Gamma	[17]
Costs			
Drug costs			
Warfarin therapy			
Daily cost for 5 mg/day	$0.22	Fixed	[7]
Monthly fee for INR counselling	$11.77 (SE: 1.18)^	Gamma	[10]
LMWH therapy (dalteparin)			
Month 1 daily cost (200 IU/kg/day)*	$35.00	Fixed	[7]
Month 2 to 6 daily cost (150 IU/kg/day)*	$28.98	Fixed	[7]
Treatment costs			
ICH initial treatment	$15,595 (SE: $2816.40)	Gamma	[6]
ICH follow up	$11,149 (SE: $1114.89)	Gamma	
Acute events treatment costs			
DVT hospital costs	$6,416 (SE: $641.57)	Gamma	[3]
DVT hospital physician costs	$367.66	Fixed	[4]
DVT outpatient (tests, nursing time and monitoring)	$327 (SE: $21.45)	Gamma	[5]
DVT outpatient physician			

Input	Value (SE/95% CI/IQR)	Distribution	Source
costs			
	$141	Fixed	4
DVT outpatient drug costs			
PE hospital costs	$251	Fixed	7
PE hospital physician costs			
	$6,209 (SE: $620.91)	Gamma	3
Major bleed hospital costs	$358	Fixed	4
Major bleed hospital physician costs	$4,531 (SE: $453.06)	Gamma	3
Minor bleed on warfarin (includes INR test)	$246	Fixed	4
	$146.73	Fixed	7,9
Minor bleed on lmwh			
	$72.33	Fixed	7,9
Physician visits			
Hematologist visit	$79.85 assessment, $61.25 reassessment	Fixed	4
GP visit	$35.50	Fixed	4
Nurse visit (1 hour in home)	$55.00 (SE: 5.5)^	Gamma	8
Laboratory tests			
INR	$6.20	Fixed	9
CBC	$8.27	Fixed	
Liver function tests	$7.76	Fixed	
Creatinine	$2.56	Fixed	
Collection fee	$7.76	Fixed	

Note: ^SE is estimated as 10% of mean
#SE is estimated as 50% of mean
~Beta distribution with assumed sample size of 10
*based on 75 kg adult

Exhibit 20: Data Estimates Specific To Decision Analytic Model 1

Input	Value	Distribution	Source
Clinical Parameters			
Recurrent venous thromboembolism			
With warfarin, %	16%	Beta (53, 283)	
With lmwh, %	8%	Beta (27, 309)	
Probability that VTE is a DVT			
With warfarin, %	70%	Beta (37, 16)	17
With LMWH, %	52%	Beta (14, 13)	
Probability that VTE is a PE			
With warfarin, %	30%	Calculated	
With LMWH, %	48%	Calculated	
Probability that a pulmonary embolism is fatal			
With warfarin, %	44%	Beta (7, 9)	17
With lmwh, %	38%	Beta (5, 8)	
Probability of any bleed			
With warfarin, %	19%	Beta (64, 271)	17
With LMWH, %	14%	Beta (47, 291)	
Probability that bleed is a major bleed			
With warfarin, %	19%	Beta (12, 52)	17
With LMWH, %	40%	Beta (19, 28)	
Probability that bleed is a minor bleed			17

Input	Value	Distribution	Source
Clinical Parameters			
With warfarin, %	81%	Calculated	
With LMWH, %	60%	Calculated	
Death due to causes other than PE			
With warfarin, %	38%	Beta (129, 207)	[17]
With LMWH, %	37%	Beta (125, 211)	
Major bleed is ICH	9%	Beta (24, 252)	[19]

Exhibit 21: Data Estimates Specific To Decision Analytic Model 2

Input	Value (95% CI)	Distribution	Source
Clinical Parameters			
Warfarin probabilities			
Recurrent venous thromboembolism	16%	Beta (53, 283)	
Probability of any bleed	19%	Beta (64, 271)	[17]
Probability that bleed is major	19%	Beta (19, 28)	
Probability that bleed is minor	81%	Calculated	
Probability of death (all causes)	40%	Beta (136, 200)	
Relative risks for LMWH versus warfarin			
Recurrent venous thromboembolism	0.51 (0.35, 0.71)	Lognormal	
Major bleed	1.07 (0.52, 2.19)	Lognormal	[2]
Minor bleed	0.89 (0.51, 1.55)	Lognormal	
Death (at 6 months)	0.96 (0.81, 1.13)	Lognormal	
Probability that a venous thromboembolism is a pulmonary embolism	36%	Beta (29, 51)	[17]
Probability that a venous thromboembolism is a DVT alone	64%	Calculated	
Major bleed is ICH	9%	Beta (24, 252)	[19]

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