TITLE: Low-Molecular Weight Heparins versus Warfarin for the Long-term Prevention or Treatment of Deep Vein Thrombosis or Pulmonary Embolism

DATE: 27 May 2013

CONTEXT AND POLICY ISSUES

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two significant healthcare concerns related to one single coagulation disorder: venous thromboembolism (VTE).\(^1,2\) DVT usually occurs in the lower extremities, but the thrombus may dislodge and travel to the lungs to cause PE, which is associated with increased morbidity and mortality.\(^1\) Various inherited or acquired risk factors and disorders result in a state of hypercoagulability and may increase the occurrence of VTE, especially when several combine in a given patient.\(^3\) Some of the most frequently encountered risk factors include malignancy, trauma or surgery, pregnancy, inherited thrombophilia, and use of pro-thrombotic medications; however, having experienced a previous VTE episode probably is the most significant risk factor for recurrent VTE.\(^3\)

Anticoagulation is the cornerstone of VTE primary prevention in at-risk patients, as well as VTE treatment and subsequent secondary prevention.\(^1,2\) Anticoagulants aim at preventing further thrombus extension, avoid VTE recurrence and preclude the development of complications;\(^1,2\) but also lead to an increased risk of bleeding complications. In most uncomplicated cases, the American College of Chest Physicians 2012 Clinical Practice Guidelines\(^1\) recommend oral anticoagulation using a vitamin K antagonist such as warfarin, with initial anticoagulation achieved through parenteral treatment with low molecular weight heparins (LMWHs), fondaparinux or unfractionated heparin.\(^1\) Newer oral anticoagulants are currently recommended as alternatives to the aforementioned treatment options; emerging evidence will likely help define their place in therapy.\(^1\) In some particular populations, such as in the presence of cancer or in patients who are unable to use warfarin, extended anticoagulation with LMWH is the preferred treatment option.\(^1,2\) Treatment durations vary according to the nature of the risk factors for VTE. While orthopedic surgery usually warrants anticoagulation for 35 days or less,\(^4\) treatment of a VTE episode and subsequent prevention should be maintained for a minimum of 3 months; however, extending anticoagulant therapy beyond that proves beneficial for patients with persistent risk factors, or experiencing recurrent or unprovoked idiopathic VTE.\(^1\)

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This Rapid Response report aims to provide further information regarding the comparative clinical and cost-effectiveness of LMWHs versus warfarin for long-term treatment and prevention of DVT and/or PE. This will inform decision-making regarding the reimbursement criteria of LMWHs in a participating jurisdiction.

RESEARCH QUESTIONS

1. What is the comparative clinical efficacy of LMWHs versus warfarin for long-term (>35 days) primary prevention of DVT and/or PE?

2. What is the cost-effectiveness of LMWHs versus warfarin for long-term (>35 days) primary prevention of DVT and/or PE?

3. What is the comparative clinical efficacy of LMWHs versus warfarin for long-term (>35 days) treatment and secondary prevention of DVT and/or PE?

4. What is the cost-effectiveness of LMWHs versus warfarin for long-term (>35 days) treatment and secondary prevention of DVT and/or PE?

KEY FINDINGS

There was no evidence in the literature searched pertaining to the clinical or cost-effectiveness of LMWHs versus warfarin for long-term primary prevention of VTE. However, findings from four publications comparing the clinical efficacy and cost-effectiveness of LMWHs versus warfarin for long-term treatment and secondary prevention of VTE suggest that LMWHs may be as effective as warfarin to prevent recurrent VTE, and more effective than warfarin in a specific population of cancer patients, without increasing the risk of bleeding. However, findings should be interpreted in light of the various limitations identified. Despite higher acquisition costs, dalteparin may be cost-effective compared to warfarin in cancer patients; no economic evidence was identified for other individual agents.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 4), 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, randomized controlled trials and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2003 and April 29, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.
Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients at risk or being treated for DVT and/or PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>LMWHs, used alone as a single agent, for &gt;35 days:</td>
</tr>
<tr>
<td></td>
<td>• Dalteparin</td>
</tr>
<tr>
<td></td>
<td>• Enoxaparin</td>
</tr>
<tr>
<td></td>
<td>• Nadroparin</td>
</tr>
<tr>
<td></td>
<td>• Tinzaparin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Warfarin, used at an appropriate dosage, for &gt;35 days</td>
</tr>
<tr>
<td>Outcomes</td>
<td>• Clinical effectiveness</td>
</tr>
<tr>
<td></td>
<td>• Adverse events</td>
</tr>
<tr>
<td></td>
<td>• Cost-effectiveness</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health Technology Assessment / Systematic reviews / Meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td></td>
<td>Economic evaluations</td>
</tr>
</tbody>
</table>

DVT = Deep vein thrombosis; LMWHs = Low molecular weight heparins; PE = Pulmonary embolism.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2003, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

We elected to assess the quality of included systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. For included randomized controlled studies, the assessment tool selected was the SIGN 50 checklist. We chose not to calculate a numeric score for each study, but to instead summarize and describe strengths and weaknesses of each study. Economic studies were assessed for completeness of reporting of the model, model inputs, data sources, and disaggregated results, and the sensitivity analyses conducted, based on the British Medical Journal Checklist for economic studies.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 259 citations were identified in the literature search. Following screening titles and abstracts, 230 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. Of the 29 potentially relevant reports, 19 publications were excluded for various reasons, while 10 publications met the inclusion criteria. However, six of these 10 publications were excluded as well since they were referenced in at least one selected systematic review, resulting in the final inclusion of four publications in this report, consisting of two clinical systematic reviews and two economic evaluations. Appendix 1 describes the PRISMA flowchart of the study selection for this review.
A. Clinical efficacy of LMWHs versus warfarin for long-term primary prevention of VTE

No publication comparing the clinical efficacy of LMWHs versus warfarin for long-term primary prevention of VTE met the inclusion criteria and could be included in this review.

B. Cost-effectiveness of LMWHs versus warfarin for long-term primary prevention of VTE

No publication comparing the cost-effectiveness of LMWHs versus warfarin for long-term primary prevention of VTE met the inclusion criteria and could be included in this review.

C. Clinical efficacy of LMWHs versus warfarin for long-term treatment and secondary prevention of VTE

Summary of Study Characteristics

The two clinical systematic reviews included in this report addressed the question of comparative clinical efficacy of LMWHs versus warfarin for long-term treatment and secondary prevention of VTE. Therefore, the populations included in these studies consisted of patients experiencing DVT and/or PE and requiring long-term VTE prevention due to the presence of various risk factors, including cancer (Noble 2008). Interventions evaluated in individual studies included dalteparin, enoxaparin and tinzaparin, which were compared to warfarin or in some cases acenocoumarol, another vitamin K antagonist (VKA) available but rarely used in Canada. Treatment durations all ranged from 3 to 6 months. The most common outcomes measured included mortality, recurrent VTE and bleeding. Details on study characteristics of the two clinical systematic reviews included in this report figure in Table 2.

Table 2: Summary of Systematic Reviews

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Key inclusion criteria, N studies</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>McManus 2011</td>
<td>Patients with DVT / PE. N=3 studies (2 SRs; 1 RCT) including a total of 2907 patients</td>
<td>Long-term LMWHs</td>
<td>Long-term VKA</td>
<td>Efficacy: Mortality, symptomatic VTE recurrence. Harms: Major hemorrhage.</td>
</tr>
<tr>
<td>Noble 2008</td>
<td>Patients with DVT / PE and advanced cancer. N=4 studies (4 RCTs) including a total of 1224 patients</td>
<td>Long-term LMWHs</td>
<td>Long-term warfarin</td>
<td>Efficacy: Recurrent VTE. Harms: Bleeding.</td>
</tr>
</tbody>
</table>

LMWH = Low molecular weight heparins; RCTs = Randomized controlled trials; SRs = Systematic reviews; VKA = Vitamin K antagonist.

Note: Long-term treatment is defined as >35 days.

Summary of Critical Appraisal

The critical appraisal of the included clinical systematic reviews is summarized in Table 3. Overall, the systematic reviews conducted comprehensive literature searches with no or minimal restrictions. Scientific quality of included studies was assessed and used appropriately in formulating recommendations. However, methods used to identify, extract, and summarize
studies were not consistently described; in addition, there was limited reporting of study characteristics. The likelihood of publication bias was not assessed, nor was a list of excluded studies provided.

Both systematic reviews included in this report evaluated the clinical benefits of LMWHs as a class and therefore, pooled the findings obtained for individual agents. McManus 2011\textsuperscript{8} included studies with both warfarin and acenocoumarol as a comparator. The dosages of medication used in the individual studies were not typically reported, precluding adequate judgment on their appropriateness from a Canadian clinical practice perspective.

### Table 3: Summary of Critical Appraisal of Individual Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| McManus 2011\textsuperscript{8} | • Comprehensive literature search of multiple databases based on pre-defined criteria; no limits on language.  
• Scientific quality of included studies assessed using GRADE, and quality of evidence used appropriately in formulating conclusions.  
• Conflicts of interest stated. | • Few details provided regarding methods for selecting studies, and for quality assessment and data synthesis, though these were likely robust.  
• Inclusion of reports limited to systematic reviews of RCTs and RCTs, blinding required for inclusion unless impossible.  
• No list of excluded studies provided.  
• Limited reporting of study characteristics.  
• Publication bias not assessed. |
| Noble 2008\textsuperscript{9} | • Comprehensive literature search of multiple databases based on pre-defined criteria; no limits on language.  
• Duplicate data extraction performed; appropriate description of methods used to combine findings.  
• Scientific quality of included studies assessed using standard criteria requested by the Association for Palliative Medicine of Great Britain and Ireland, and quality of evidence used appropriately in formulating conclusions.  
• Conflicts of interest stated. | • Prospective design and duplicate study selection unclear.  
• No list of excluded studies provided.  
• Limited reporting of study characteristics.  
• No individual reporting of scientific quality of included studies, although assessed to grade conclusions.  
• Publication bias not assessed. |

GRADE = Grading of Recommendations Assessment, Development and Evaluation working group; RCTs = Randomized controlled trials.

### Summary of Findings

The key study findings are summarized in Table 4.

#### Clinical effectiveness

The McManus 2011\textsuperscript{8} systematic review did not include a meta-analysis; therefore, the results of individual studies were not pooled. Findings from one systematic review and one RCT suggested the absence of a significant difference between a 3 to 6-month treatment with LMWHs compared to oral anticoagulation with a VKA for a similar duration in terms of mortality or recurrent VTE after 3 to 12 months of follow-up;\textsuperscript{12,13} however, whether individual studies had sufficient power to detect a statistically significant difference between treatment arms is
unknown. One systematic review suggested that LMWHs may be superior to VKAs to prevent recurrent VTE 3 to 6 months after the initial event.\textsuperscript{14} Nevertheless, the authors concluded in favor of a similar clinical effectiveness between LMWHs and oral anticoagulation with a VKA.\textsuperscript{8}

Findings from the Noble 2008\textsuperscript{9} systematic review and meta-analysis suggested however that LMWHs are more effective than warfarin to prevent recurrent VTE in cancer patients, as the pooled estimate reached statistical significance (Table 4). No data was available from this publication with regard to mortality. Authors conducted the meta-analysis using a fixed-effect model; heterogeneity in the pooled estimate was however not reported.

Therefore, there is some level of inconsistency between the two systematic reviews included in the report for clinical effectiveness; however, the two were conducted in a different population (overall population of patients with VTE\textsuperscript{8} versus cancer patients only\textsuperscript{9}). It is likely that the two populations present with different characteristics, especially when it comes to individual risk factors for VTE. Evaluating LMWHs as a class, without regard to the dosing regimen used for both the interventions and comparators, may also affect the generalizability of the findings to real-life Canadian practice.

\textit{Adverse events}

Both clinical systematic reviews included here reported bleeding as the only harms outcome and in both publications, findings suggested that the risk of bleeding was not statistically significantly different between LMWHs and oral anticoagulation with a VKA. In McManus 2011,\textsuperscript{8} there was a trend in some studies for LMWHs to be potentially associated with fewer bleeding events than VKAs; however, the authors concluded the effectiveness of these agents may be equal based on very low-quality evidence.\textsuperscript{8}

Bleeding definitions for event inclusion in the individual studies were not provided; as a result, it is possible that the type of bleeding events included vary substantially among studies (e.g., minor bleeding versus major hemorrhage). The absence of statistical significance between LMWHs and oral anticoagulation with a VKA should be viewed as inconclusive, and does not guarantee that the risk of bleeding is similar. Trials may not have had sufficient power to detect a statistically significant difference between treatments, and it is not possible with the information provided to assess whether other methodological flaws may have impacted the results.
Table 4: Summary of Findings

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Relevant study characteristics</th>
<th>Outcomes</th>
<th>Mortality</th>
<th>Recurrent VTE</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>McManus 2011</td>
<td>Population: Any patient with VTE (N=2907)</td>
<td>Van Der Heijden 2011, SR, N = 7 studies (1137 patients)</td>
<td>OR = 1.51 [95% CI 0.77, 2.97] at 3-6 months</td>
<td>OR = 0.70 [95% CI 0.42, 1.16] at 3-6 months</td>
<td>All trials: OR = 0.38 [95% CI 0.15, 0.94] Clear concealment: OR = 0.80 [95% CI 0.21, 3.00]</td>
</tr>
<tr>
<td></td>
<td>Interventions: LMWHs (dalteparin, enoxaparin, tinzaparin) vs. VKA (warfarin, acenocoumarol) for 3-6 months</td>
<td>Ferretti 2006, SR, N = 11 studies (2907 patients)</td>
<td>Not reported</td>
<td>RR = 0.63 [95% CI 0.47, 0.83] at 3-6 months</td>
<td>RR = 1.29 [95% CI 0.87, 3.14] at 6-12 months</td>
</tr>
<tr>
<td></td>
<td>A meta-analysis was not performed; results are reported for each individual study.</td>
<td>Daskalopoulos 2005, RCT, (108 patients)</td>
<td>Not reported</td>
<td>Reported in 6% of LMWH patients vs 10% with VKA at 12 months; reported as not significant.</td>
<td>Reported in 4% of LMWH patients vs 8% with VKA; reported as not significant.</td>
</tr>
</tbody>
</table>

Authors’ Conclusions

“Mortality: Compared with long-term oral anticoagulation, long-term LMWH is as effective at reducing mortality at 3 months (high-quality evidence).

Rate of symptomatic recurrence: Compared with long-term oral anticoagulation, long-term LMWH is as effective at reducing recurrence of thromboembolism at 3 to 12 months (low-quality evidence).

Adverse effects: major haemorrhage: Long-term LMWH and long-term oral anticoagulation may be equally likely to cause major haemorrhage (very low-quality evidence).” (pp. 8)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Relevant study characteristics</th>
<th>Mortality</th>
<th>Recurrent VTE</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noble 2008</td>
<td>Population: Patients with VTE and cancer (N=1224)</td>
<td>Not reported</td>
<td>RR = 0.51 [95% CI 0.35, 0.74] p &lt; 0.0001</td>
<td>RR = 1.10 [95% CI 0.77, 1.58] p = 0.6</td>
</tr>
<tr>
<td></td>
<td>Interventions: LMWHs (dalteparin, enoxaparin, tinzaparin) vs. warfarin for 3-6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Authors’ Conclusions

“Long-term full-dose LMWH should be the drug of choice in the secondary prophylaxis of venous thromboembolism in patients with cancer of any stage, performance status, or prognosis (grade A, level Ib).” (pp. 582)

“Data from these RCTs suggest that long-term LMWH is more effective than warfarin in decreasing the risk of recurrent venous thromboembolism in patients with cancer and, on this basis, we suggest that LMWH is considered as the treatment of choice for the secondary prophylaxis of venous thromboembolism. The risk of bleeding with long-term LMWH seems to be similar to that with warfarin in the cancer populations studied.” (pp. 582)

CI = Confidence interval; LMWH = Low molecular weight heparin; OR = Odds ratio; RCT = Randomized controlled trial; RR = Relative risk or risk ratio; SR = Systematic review; VKA = Vitamin K antagonist; VTE = Venous thromboembolism.
D. Cost-effectiveness of LMWHs versus warfarin for long-term treatment and secondary prevention of VTE

Summary of Study Characteristics

The two economic evaluations included in this report addressed the question of comparative cost-effectiveness of LMWHs versus warfarin for long-term treatment and secondary prevention of VTE. Both studies were cost-utility analyses (CUA) with a time horizon of 6 months; one was conducted from a Canadian health care system perspective while the other took a US societal perspective. The studies evaluated the cost-effectiveness of dalteparin versus warfarin; no studies were found with regard to the other LMWHs. Details on study characteristics of the two economic evaluations included in this report figure in Table 5.

Table 5: Summary of Economic Evaluations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of Economic Evaluation</th>
<th>Study Perspective</th>
<th>Patient Population</th>
<th>Intervention and Comparator</th>
<th>Assumptions</th>
</tr>
</thead>
</table>
| Dranitsaris 2006\textsuperscript{10} | CUA, benefits and health care resource utilization from the CLOT trial database (Lee 2003)\textsuperscript{15}. | Canadian health care system perspective. | Cancer patients with a newly diagnosed VTE. | Intervention: Dalteparin for 6 months  
Comparator: Warfarin for 6 months | • Findings from the CLOT trial\textsuperscript{15} are generalizable to Canadian clinical practice.  
• Health care utilization data for bleeding events and recurrent VTE from the literature are realistic.  
• Utility assessments gathered from oncology nurses and pharmacists are representative of those from actual patients. |
| Aujesky 2005\textsuperscript{11} | CUA, decision analytic model. | US societal perspective. | Hypothetical cohort of patients aged 65 with cancer and VTE. | Intervention: Dalteparin for 6 months  
Comparator: Warfarin for 6 months | • All patients were at risk for death, bleeding and VTE. Probabilities to experience these events depended on treatment received.  
• Bleeding led to transient discontinuation of therapy, unless it was intracranial.  
• Patients who survived 6 months after VTE were at risk for late complications. |

CLOT = Comparison of Low molecular weight heparin versus Oral anticoagulant Therapy for long term anticoagulation in cancer patients with venous thromboembolism trial; CUA = Cost-utility analysis; US = United States; VTE = Venous thromboembolism.
Summary of Critical Appraisal

Both economic evaluations used robust methods to conduct their respective analysis. Model designs and data sources, model inputs, and disaggregated results were clearly reported. Sensitivity analyses were conducted to assess the robustness of the findings to various changes in assumptions, and limitations of the analyses were clearly described. However, none of the included evaluations gathered health state and other benefits valuation from actual patients. In addition, Aujesky\textsuperscript{11} was conducted using a US perspective; therefore, the generalizability of this evaluation to Canadian clinical practice is uncertain.

Table 6: Summary of Critical Appraisal of Individual Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Dranitsaris 2006\textsuperscript{10} | • Study design, data sources and disaggregated results clearly reported.  
• Appropriate source of effectiveness estimates.  
• Methods for the estimation of unit cost described.  
• Included cost of AEs (bleeding).  
• Quantities of resources reported separately from their cost.  
• Approach and choice of variables for sensitivity analyses are justified.  
• Limitations of the evaluation presented. | • Health state and other benefits valuation obtained from health care professionals rather than from actual patients.  
• Time horizon and discounting of costs and benefits unclear.  
• Costs and resources collected as part of RCT may not reflect clinical practice. |
| Aujesky 2005\textsuperscript{11} | • Model design and data sources, model inputs, and disaggregated results clearly reported.  
• Appropriate source of effectiveness estimates.  
• Methods for the estimation of unit cost described.  
• Included cost of AEs (bleeding).  
• Discounted future costs and benefits.  
• Approach and choice of variables for sensitivity analyses are justified.  
• Limitations of the evaluation presented. | • Quantities of resources used for various health states not reported.  
• Health state and other benefits valuation calculated without interview of patients or patients’ surrogate.  
• Cost of productivity loss not reported separately.  
• Evaluation conducted in a US perspective presents a generalizability issue versus clinical practice in Canada. |

RCT = Randomized controlled trial; US = United States.

Summary of Findings

The key study findings are summarized in Table 7.

The two cost-utility analyses reported incremental cost per quality adjusted life years (QALY) for the use of dalteparin compared to warfarin of 13,751$Can,\textsuperscript{10} from the Canadian health care system perspective and of 149,865$US,\textsuperscript{11} from a US societal perspective (Table 7).

Dranitsaris 2006\textsuperscript{10} found that the cost of drug therapy for patient administered dalteparin was the largest cost contributor, whereas VTE treatment and laboratory monitoring were a major source of expenditures in patients receiving warfarin.\textsuperscript{10} The utility associated with the use of dalteparin that was gathered from oncology nurses and pharmacists was twice that of warfarin,
resulting in the assumption that dalteparin had a substantially favorable impact on quality of life. Sensitivity analyses performed suggested that the estimated cost per QALY gained was relatively stable despite variations in the cost differential between treatments and in the health months equivalent scores used to estimate utility results.

Aujesky also found that treatment with dalteparin was more expensive than warfarin, mainly due to drug acquisition cost. However, in order to express the utilities associated with each treatment, authors estimated the number of days of utility lost because of hospitalization due to acute complications, which resulted in a small incremental quality-adjusted life expectancy of 0.051 QALYs between treatments. Unlike the first economic evaluation presented, this analysis assumed that improvement in quality of life with the use of dalteparin was minimal. Sensitivity analyses performed suggested that results were robust, though sensitive to early mortality risks and utility values associated with each treatment.

The dosage of dalteparin used in both economic evaluations was consistent with the Health Canada recommended dosage for this agent for VTE treatment and long-term secondary prevention. However, Dranitsaris suggested that the Canadian cost of dalteparin is considerably lower than the US cost for this agent, and that this may explain in part the substantial difference in terms of the respective incremental cost-effectiveness ratio reported in the two publications.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of evaluation</th>
<th>Intervention / comparator</th>
<th>Economic model</th>
<th>Key results [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dranitsaris 2006</td>
<td>CUA Canadian health care system perspective*</td>
<td>Dalteparin 200 IU/kg/day x 1 month, then 150 IU/kg/day. vs Adjusted-dose warfarin (target INR 2.5). For 6 months in cancer patients.</td>
<td>Benefits and health care resource utilization data collected from the CLOT trial database.†</td>
<td>Mean cost/patient:† Dalteparin = 4,162$ Warfarin = 2,003$ Cost/VTE avoided: 27,700$ [24,400$ – 30,400$] ICER (cost/QALY): 13,751$ [12,400$ – 15,100$]</td>
</tr>
<tr>
<td>Aujesky 2005</td>
<td>CUA US societal perspective§ over lifetime period</td>
<td>Dalteparin 200 IU/kg/day x 1 month, then 150 IU/kg/day. vs Adjusted-dose warfarin (target INR 2.5). For 6 months in cancer patients.</td>
<td>Decision analytic model (probability distributions generated via Monte Carlo iterations)</td>
<td>Overall cost/patient:* Dalteparin = 15,329$ Warfarin = 7,720$ ICER (cost/QALY): 149,865$</td>
</tr>
</tbody>
</table>

CLOT = Comparison of Low molecular weight heparin versus Oral anticoagulant Therapy for long term anticoagulation in cancer patients with venous thromboembolism trial; CUA = Cost-utility analysis; ICER = Incremental cost-effectiveness ratio; IU = International units; QALY = Quality adjusted life years; US = United-States.

* Canadian dollars, year 2005 values.
† Lee 2003;§ n=676 randomized patients.
‡ Includes cost of drug therapy and health care resource utilization.
§ US dollars, year 2002 values.
¥ Includes cost of drug therapy, health care resource utilization and indirect costs for patients (transportation expenses and value of time lost based on the average hourly wage of a US nonfarm production worker in 2002).
Limitations

No evidence comparing the clinical efficacy or cost-effectiveness of LMWHs versus warfarin for long-term primary prevention of VTE was identified and could be included in this review.

A total of 4 publications were identified that compared the clinical efficacy and cost-effectiveness of LMWHs versus warfarin for long-term treatment and secondary prevention of VTE. From the clinical perspective, two clinical systematic reviews were included and described in this report. Both appeared methodologically rigorous; however, there was limited reporting of study characteristics. As a result, only limited data were available pertaining to patient populations included in the individual studies, as well as with regard to interventions’ dosages and regimens evaluated. No evidence was identified in the literature pertaining to nadroparin. Other LMWHs were considered as a class and results were aggregated regardless of the specific agent used. The same applied to VKAs, where individual studies using warfarin or acenocoumarol as a comparator were considered by the publications as a homogenous group. This inadequate reporting of study characteristics precluded adequate judgment on the appropriate use of each agent in the individual trials based on Canadian clinical practice.

From the economic perspective, two economic evaluations were included and described in this report, both evaluating the cost-effectiveness of dalteparin compared to warfarin. Therefore, no data was available for enoxaparin, nadroparin of tinzaparin. One was conducted from a Canadian health care system perspective, but collected costs and resources as part of an RCT. Although providing good quality evidence, this type of study design may not be reflective of clinical practice. The other economic evaluation included was conducted from a US perspective, and estimated costs based on the US health care system and US dollar. Therefore, the generalizability of this evaluation to Canadian clinical practice is also uncertain.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There was no evidence in the literature searched pertaining to the clinical or cost-effectiveness of LMWHs versus warfarin for long-term primary prevention of VTE. However, a total of four publications were identified that compared the clinical efficacy and cost-effectiveness of LMWHs versus warfarin for long-term treatment and secondary prevention of VTE: two clinical systematic reviews and two economic evaluations. Findings suggested that long-term treatment with LMWHs may be as effective as warfarin to prevent mortality and recurrent VTE in a general population of patients who experienced DVT and/or PE. In a specific population of cancer patients, LMWHs may be more effective than warfarin to prevent recurrent VTE; however, no data on mortality was reported. Findings also suggested that LMWHs and warfarin likely had a similar risk of bleeding. However, these results should be interpreted with caution. The included systematic reviews acknowledged that these conclusions were based on various levels of evidence quality. In addition, the absence of statistical significance between treatments does not guarantee that their effect is similar, and it is unknown whether studies had sufficient power to detect a statistically significant difference between treatments. Despite higher acquisition costs, dalteparin may be cost-effective compared to warfarin in cancer patients; no economic evidence was identified for other individual agents.
REFERENCES


APPENDIX 1: Selection of Included Studies

259 citations identified from electronic literature search and screened

230 citations excluded

29 potentially relevant articles retrieved for scrutiny (full text, if available)

0 potentially relevant reports retrieved from other sources (grey literature, hand search)

29 potentially relevant reports

25 reports excluded:
- irrelevant study design (9)
- irrelevant intervention/comparator (8)
- already included in at least one of the selected systematic reviews (6)
- irrelevant outcomes (1)
- other (1)

4 reports included in review

LMWH versus Warfarin for DVT / PE

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