

Low Molecular Weight Heparins

FINAL CONSOLIDATED COMPREHENSIVE RESEARCH PLAN

September 2015

A. Introduction

The objective of the drug class review on LMWH is to provide evidence-informed recommendations for the use of low molecular weight heparins (LMWHs) through the publicly funded drug program in Ontario. This comprehensive review will include:

- systematic critical appraisal of evidence-based guidelines,
- reimbursement-based analyses and de novo economic evaluation (if needed),
- drug utilization studies using administrative claims data from Ontario and across Canada,
- environmental scans of national and international drug policies,
- contextualization of the available evidence and experience from other regions, with consideration given to health equity,
- qualitative analyses of perspectives of prescribers,
- identification of barriers to, and enablers of, successful policy implementation,
- recommendation of potential drug reimbursement models.

B. Research Questions

Patient population and inclusion criteria

Use of low molecular weight heparin in the following indications:

- Treatment of deep vein thrombosis (non-cancer patients);
- Treatment of deep vein thrombosis in patients in whom treatment with warfarin is not tolerated, or is contraindicated;
- Treatment of deep vein thrombosis in patients who have failed treatment with warfarin;
- Treatment of deep vein thrombosis in pregnant or lactating females; and,
- Treatment of symptomatic acute venous thromboembolism in patients with cancer.
- Post-operative prophylaxis of deep vein thrombosis for patients with hip or knee surgery who cannot use warfarin; and,
- Post-operative prophylaxis of venous thromboembolism in patients undergoing orthopedic surgery of the lower limbs (e.g., hip, knee)
- Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery;
- The prevention (primary and secondary) of venous thromboembolism in patients with cancer; and,
- The prevention of venous thromboembolism in non-orthopedic surgical patients.

Drugs of interest

- Dalteparin
- Enoxaparin
- Nadroparin
- Tinzaparin
- Fondaparinux

Comparator(s)

Comparators include: heparin, warfarin, direct oral anticoagulant (DOAC), LMWHs, mechanical intervention (depending on the indication for treatment or prophylaxis)

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	<p>What is the perceived effectiveness of low molecular weight heparins?</p> <p>What is the impact of LMWH on perceived quality of life?</p> <p>What is the experience of prescribing these therapies?</p> <p>To what extent are the policy recommendations feasible and acceptable?</p>
Systematic Reviews and Network Meta-Analyses	Systematic Review Unit	<p>What are the guidelines for the use of low molecular weight heparins (LMWH) for the approved treatment indications in the Province of Ontario?</p> <p>What are the guidelines for the use of LMWH for the approved post-operative prophylaxis indications in the Province of Ontario?</p> <p>What are the guidelines for the use of LMWH for:</p> <ul style="list-style-type: none"> • Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery; • The prevention of venous thromboembolism in patients with cancer; and, • The prevention of venous thromboembolism in non-orthopedic surgical patients.
Environmental Scan and Barriers to Implementation Local and Historical Context	Formulary Modernization Unit	<p>How are LMWHs currently being accessed in publicly funded programs across Canada as well as internationally?</p> <p>What is the impact of different reimbursement schemes for LMWHs on patient access, quality of life and/or utilization and costs?</p> <p>Does sex, gender or socioeconomic status play an important role in any of the analyses described?</p>
Costs and Utilization Trends	Pharmacoepidemiology Unit	<p>To examine national and provincial trends in use of anticoagulants across Canada</p> <p>To perform cross provincial comparisons of the trends in low molecular weight heparin (LMWH) utilization in public drug programs across Canada</p> <p>To investigate trends of prescribing for publicly-funded low molecular weight heparins in Ontario</p> <p>To investigate characteristics of publicly-funded low molecular weight heparin use among newly initiated users in Ontario</p> <p>To investigate the duration of publicly-funded low molecular weight heparin use among newly initiated users in Ontario</p> <p>To report the number of accepted submissions for public drug funding for low molecular weight heparins in Ontario</p>
Health Equity	All units	<p>Does sex/gender, age, geographical location (e.g., rural vs. urban) or socioeconomic status play an important role in any of the</p>

Proposal	Research unit	Research question(s)
Reimbursement -based Economics	Pharmacoeconomics Program	<p>analyses described?</p> <ul style="list-style-type: none"> • 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 <i>prevention</i> of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer? • What is the current evidence for the comparative cost-effectiveness of LMWH, as compared with each other, warfarin, mechanical intervention, parenteral anticoagulation or placebo, for the <i>treatment</i> of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer? • If necessary and feasible, based on a de novo economic model, what is the comparative cost-effectiveness of LMWH, as compared with each other, warfarin, mechanical intervention, parenteral anticoagulation or placebo, for the <i>prevention</i> of DVT or PE in patients with cancer? • If necessary and feasible, based on a de novo economic model, what is the comparative cost-effectiveness of LMWH, as compared with each other, warfarin, mechanical intervention, parenteral anticoagulation or placebo, for the <i>treatment</i> of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer? • What is the budget impact of alternative policies for reimbursing LMWH for the <i>prevention</i> of DVT or PE in patients with cancer? • What is the budget impact of alternative policies for reimbursing LMWH for the <i>treatment</i> of DVT or PE in patients with cancer? • If necessary and feasible, what is the impact of alternative policies for reimbursing LMWH for indications other than those listed above? • If necessary and feasible, based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing LMWH for the <i>prevention</i> of DVT or PE in patients with cancer? • If necessary and feasible, based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing LMWH for the <i>treatment</i> of DVT or PE in patients with cancer?

C. Specific Proposals

The Drug Class Review is comprised of five different reviews, namely the Qualitative Research Unit, Systematic Review Unit, Pharmacoepidemiology Unit, Environment Scan/local and historical context and Pharmacoeconomics Unit. Further information on each of the proposals is can be found on our website: www.odprn.ca

1. Qualitative Review Unit

Objectives:

- To explore factors related to the experience of prescription and use of LMWH
- To determine the social acceptability of reimbursement policy recommendations for LMWH

Study Questions:

- What is the perceived effectiveness of LMWH?
- What is the impact of LMWH on perceived quality of life?
- What is the experience of prescribing these therapies?
- To what extent are the policy recommendations feasible and acceptable?

Phase 1: Exploration of factors affecting the dispensing and utilization of LMWH

Study Design – This phase will use a qualitative framework approach to guide the data collection and analysis processes. One-on-one interviews and accompanying field notes will be the primary and secondary data sources, respectively.

Study Population – Identified stakeholders for the LMWH review include 1) primary care physicians; 2) pharmacists; 3) hematologists; 4) internal medicine; 5) emergency medicine and 5) oncologists

Methods – A purposive sampling approach using a convenience sample will be used in order to elicit the specific perceptions and opinions of those who will be involved in or affected by drug policy decisions. Clinicians will be recruited through circles of contact, professional networks and snowball recruitment. Publicly available contact information will also be searched to develop contact lists. An ODPRN member or study coordinator will make contact with clinicians by phone, e-mail or fax. General calls for recruitment of all eligible groups will be placed in professional newsletters, e-blasts and social media (Twitter, Facebook). We will aim to recruit 2-3 participants from each group or until saturation of themes is met.

Outcomes:

- Experiences accessing LMWH
- Experiences treating patients with LMWH
- Perceived safety and effectiveness of LMWH
- Perceived barriers to access and health equity issues
- Any unanticipated issues related to LMWH

Phase 2: Assessment of the social acceptability of recommended policy actions related to LMWH

Study Design – RAND Appropriateness Method and Survey

Study Population – Representatives of the general public; stakeholder groups (i.e. among the groups described in Phase 1 above); patient advocacy groups; topic-specific interest groups; and industry

Methods – Members of the general public will be recruited to participate in a meeting/webinar to rate or prioritize a series of questions, discuss these questions, then re-rate and prioritize them. An online survey will also be distributed to assess aspects of social acceptability, including affordability, accessibility, and appropriateness. Survey analysis will include descriptive statistics (e.g., mean, standard deviation, median) and thematic content analysis for open-ended questions.

Outcomes -The primary outcome of interest is the feasibility and acceptability of draft recommendations

2. Systematic Review Unit

Study Questions:

- What are the guidelines for the use of low molecular weight heparins (LMWH) for the approved treatment indications in the Province of Ontario?
- What are the guidelines for the use of LMWH for the approved post-operative prophylaxis indications in the Province of Ontario?
- What are the guidelines for the use of LMWH for:
 - Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery;
 - The prevention of venous thromboembolism in patients with cancer; and,
 - The prevention of venous thromboembolism in non-orthopedic surgical patients.

Indications for Treatment or Prevention
Treatment of DVT in non-cancer patients.
Treatment of DVT in patients in whom treatment with warfarin is not tolerated, or is contraindicated.
Treatment of DVT in patients who failed treatment with warfarin.
Treatment of DVT in pregnant or lactating females.
Treatment of symptomatic acute VTE in patients with cancer.
Post-operative prophylaxis of DVT for patients undergoing hip or knee surgery (and who cannot use warfarin).
Post-operative prophylaxis of VTE in patients undergoing orthopedic surgery of the lower limbs (e.g., hip, knee).
Prevention of (prophylaxis) VTE in patients with cancer.
Prevention of (prophylaxis) VTE in non-orthopedic surgical patients.
Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery.

VTE=venous thromboembolism, DVT=deep-vein thrombosis, DOAC=direct-acting oral anticoagulant

Methods

Literature Search

We will carry out a literature search for relevant national and international treatment guidelines (North America, Europe and Australia) published since 2005 using key resources including MEDLINE, EMBASE, and The Cochrane Library databases, as well as a focused Internet and grey literature search. Additional resources or databases may be utilized if recommended by the medical librarian. No filters will be applied to limit the retrieval by study type.

Clinical experts will also be asked to identify references for the research team to supplement the database and internet search.

Article Selection

All titles and/or abstracts will be reviewed by two independent reviewers to determine eligibility. When citations meet the criteria, the full-text articles will be retrieved and reviewed.

Only guidelines published in English by professional associations, institutions or recognized medical bodies will be included. Guidelines will be included if an evidence-based development process is presented along with the levels of confidence and clinical recommendations (1). Guidelines based on expert opinion and/or consensus activities will be excluded; however, references may be retained for inclusion in the appendix of the final report to supplement higher quality guidelines. If there are updates to guidelines within the search dates employed, only the latest version of the guideline will be included.

3. Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in anticoagulant utilization

Study question: Cross-sectional analysis with quarterly time intervals

Short description of analysis: We will examine trends in use of LMWH between October 2009 and June 2015.

Analysis 2 – Cross-provincial comparisons of the trends in LMWH utilization in public drug programs

Study question: Cross-sectional analysis with quarterly time intervals

Short description of analysis: We will examine changes in LMWH prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI, Newfoundland and British Columbia between January 2014 and December 2014.

Analysis 3 – Trends in prescribing for publicly-funded LMWH in Ontario

Study question: To investigate trends in prescribing for publicly-funded LMWH use

Short description of analysis: We will look at all publicly-funded prescriptions for LMWH and determine the use of individual LU codes between April 2004 and March 2015.

Analysis 4a – Characteristics of individuals newly prescribed publically-funded LMWH use in Ontario

Study question: To characterize patients prescribed LMWH in Ontario

Short description of analysis: We will look at descriptive characteristics (January 2002-December 2012 with a minimum follow-up date of one year), including age, gender, residence (long-term care, community), socioeconomic status, prescriber of initial prescription (specialist or general practitioner), number of physician office visits within the last 1 year, past hospitalization or ED visit within the last 1 year, past medication use, indication for use

Analysis 4a – Investigate duration of publicly-funded LMWH use among newly initiated patients in Ontario

Study question: To investigate the duration of use of LMWH

Short description of analysis: We will look at the duration of LMWH use (January 2002 to December 2014). Analyses will be stratified according to Limited Use code.

Analysis 5 – Number of accepted submissions for public drug funding for LMWH in Ontario

Study questions: To report on number (%) of applications that were approved, number of EAP applications submitted, and number of indications (by drugs)

Short description of analysis: Cross-sectional study using sample EAP forms (fiscal year 2014) for LMWH

4. Pharmacoeconomic Unit

Research Questions

- 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 *prevention* of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer?
- What is the current evidence for the comparative cost-effectiveness of 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?
- If necessary and feasible, based on a de novo economic model, what is the comparative cost-effectiveness of LMWH, as compared with each other, warfarin, mechanical intervention, parenteral anticoagulation or placebo, for the *prevention* of DVT or PE in patients with cancer?
- If necessary and feasible, based on a de novo economic model, what is the comparative cost-effectiveness of 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?
- What is the budget impact of alternative policies for reimbursing LMWH for the *prevention* of DVT or PE in patients with cancer?
- What is the budget impact of alternative policies for reimbursing LMWH for the *treatment* of DVT or PE in patients with cancer?
- If necessary and feasible, what is the impact of alternative policies for reimbursing LMWH for indications other than those listed above?
- If necessary and feasible, based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing LMWH for the *prevention* of DVT or PE in patients with cancer?
- If necessary and feasible, based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing LMWH for the *treatment* of DVT or PE in patients with cancer?

Methods

RQ1 Systematic Review of Published Economic Evaluations

To address RQ1a and RQ1b, we will conduct a systematic review of the available literature on the cost-effectiveness of pharmacotherapy options for the treatment and prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer. Therapeutic options will include warfarin, mechanical prophylaxis, parenteral anticoagulation or placebo.

RQ2 De novo Economic Evaluation

If necessary and feasible, we will develop one or two de novo economic models to assess the cost-effectiveness of alternative pharmacotherapies for the treatment and prevention of DVT or PE in patients with cancer.

RQ3 Reimbursement Based Budget Impact Analysis

We will develop a model which will identify the budget impact analysis that will facilitate the reimbursement decision-making process. Emphasis will be placed on identifying the budget impact of alternative approaches to the current reimbursement status of LMWH for the treatment or prevention of DVT or PE in patients with cancer. If necessary and feasible, the impact of alternative policies for reimbursing LMWH for indications other than those listed above will be assessed, using the approach described above.

5. Environmental Scan

Research Questions

- 1. To summarize the pharmacy benefit programs for low molecular weight heparins (LMWH) in Ontario, across Canada and in select international jurisdictions**

Method: summary of available information available through the Internet; interviews with individuals at the government agencies responsible for the public drug plan

Interventions:

- Dalteparin
- Enoxaparin
- Nadroparin
- Tinzaparin
- Fondaparinux

- 2. To determine the impact of different reimbursement schemes for LMWH on patient access, quality of life and/or utilization and costs**

Method: Literature review

Intervention: various drug reimbursement schemes, including general benefits, step therapy, special authorization

Outcome(s) of interest: Indirect/direct measurements of clinical outcomes, patient satisfaction, quality of life, utilization and/or costs, functionality at work, days of productivity at work

- 3. To summarize the guidelines for prophylaxis of patients with cancer and for patients undergoing non-orthopedic surgery**

Method: Literature review

Intervention: Guidelines/recommendations for use of LMWHs as prophylaxis for patients with cancer and patients undergoing non-orthopedic surgery