

# Low Molecular Weight Heparins: Pharmacoepidemiology Unit

## COMPREHENSIVE RESEARCH PLAN

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## Objectives

1. To examine national and provincial trends in use of anticoagulants across Canada
2. To perform cross provincial comparisons of the trends in low molecular weight heparin (LMWH) utilization in public drug programs across Canada
3. To investigate trends of prescribing for publicly-funded low molecular weight heparins in Ontario
4. To investigate characteristics of publicly-funded low molecular weight heparin use among newly initiated users in Ontario
5. To investigate the duration of publicly-funded low molecular weight heparin use among newly initiated users in Ontario
6. To report the number of accepted submissions for public drug funding for low molecular weight heparins in Ontario

### Objective 1: National and Provincial Trends in Anticoagulant Utilization

**Study Design:** Cross-sectional analysis

**Study Period:** October 2009 to June 2015

**Time Intervals:** Quarterly

**Population:** All provinces

**Data Sources:** IMS Compuscript: aggregated data for all prescriptions dispensed at retail pharmacies across Canada

**Inclusion Criteria:** All privately and publicly-funded LMWH, warfarin and novel oral anticoagulant (NOACs) prescriptions dispensed in Canada

**Outcomes:**

- Number and rate of prescriptions dispensed
- Total Cost

**Report:**

1. Number of prescriptions dispensed by anticoagulant (warfarin, NOAC, LMWH), nationally
2. Number of LMWH prescriptions dispensed by drug (Enoxaparin, Tinzaparin, Nadroparin, Fondaparinux, Dalteparin) and overall cost nationally
3. Population-adjusted rate of publicly funded LMWH prescriptions by province
4. Population-adjusted rate of non-publicly (private, cash, noninsured health benefits) funded LMWH prescriptions by province

**Limitations:**

- The IMS data are only available at the prescription and unit level. Therefore, national and provincial trends in prescribing cannot determine the number of unique recipients.

## **Objective 2: Cross Provincial Comparisons of the Trends in Low Molecular Weight Heparin Utilization in Public Drug Programs**

**Study Design:** Cross-sectional analysis

**Study Period:** January 2014 to December 2014

### **Data Sources:**

- National Prescription Drug Utilization Information System Database (NPDUIS): aggregated data for all publicly funded LMWH prescriptions dispensed in Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, PEI, Newfoundland and Labrador and BC
- Ontario Drug Benefit Database (ODB): individual level data for all publicly funded prescriptions dispensed in Ontario.

**Inclusion Criteria:** All publicly-funded LMWH prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI, Newfoundland and Labrador and BC

### **Outcomes:**

- Number and rate of users
- Number of prescriptions dispensed

### **Report:**

1. Number of users, rate of users and number of prescriptions by province
2. Number of users, rate of users and number of prescriptions by province and age (<65, 65+)
3. Number of users, rate of users and number of prescriptions by province and drug (Enoxaparin, Tinzaparin, Nadroparin, Fondaparinux, Dalteparin)

### **Limitations:**

- There is no patient-level data available for publicly paid prescriptions in Quebec or the Territories. Therefore, we will be unable to make comparisons between Ontario rates and rates of use in these jurisdictions.
- Information is not available for medications dispensed in hospital.

### **Objective 3:**

## **Trends in Prescribing for Publicly-Funded Low Molecular Weight Heparins in Ontario**

**Study Design:** Cross-sectional analysis

**Study period:** April 2004 to March 2015

**Time Intervals:** Annually

**Data Sources:**

- Ontario Drug Benefit Database

**Inclusion Criteria:** All publicly-funded prescriptions for low molecular weight heparin

**Measures of Interest:**

- Number of prescriptions dispensed
- Limited Use (LU) code on ODB prescription
  - Deep venous thrombosis (DVT) (LU code 186)
  - Pregnant or lactating females (LU code 187)
  - DVT in patients whom treatment with warfarin is not tolerated (LU code 188)
  - DVT in patients who have failed treatment with warfarin (LU code 189)
  - pulmonary embolism (LU code 323)
  - post-operative prophylaxis of venous thromboembolic events in patients undergoing orthopedic surgery of the lower limbs (LU code 378 for LMWH drug fondaparinux only)
  - Other LU code
  - No LU code

**Report:**

1. Number of prescriptions by LU code on prescription annually

**Limitations:**

- The completion of the LU code in the ODB dataset is unknown. Therefore, individuals with missing LU codes may have had an LU code on their prescription that was not captured in the administrative databases. However, since some of these products are covered through the exceptional access program (EAP), we will assume that if they do not have an LU code it is most likely due to accessing these products through the EAP.
- Information is not available for medication use when hospitalized.

**Objective 4a:**  
**To Investigate Characteristics of Publicly-Funded Low Molecular Weight Heparin Use among Newly Initiated Users in Ontario**

**Study Design:** Cohort study

**Study Period:** January 2002-December 2012

**Data Sources:**

- Ontario Drug Benefit Database (ODB)
- Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)
- Canadian Institute for Health Information- National Ambulatory Care Reporting System (CIHI-NACRS)
- Ontario Health Insurance Plan Claims Database (OHIP)
- ICES Physician Database (IPDB)
- Ontario Cancer Registry (OCR)
- Mother-Baby Linked Database (MOMBABY)

**Inclusion Criteria:** All publicly-funded beneficiaries in Ontario who are newly prescribed a low molecular weight heparin

- New users aged 66 and older defined as having no prescription for a LMWH in the past 180 days
- New users  $\leq 65$  years of age defined as having a prescription for any drug in the past 181-365 days and who did not have a prescription for a LMWH in the past 180 days

**Cohort Entry Date:** Date of first prescription for a LMWH over the study period.

**Index Drug:** Defined as the LMWH drug that was prescribed on cohort entry date

**Measures of Interest:**

- Number of new users
- Age at cohort entry date (mean, SD, and by category (<65, 65+))
- Proportion of patients who were male
- Proportion of patients residing in LTC at cohort entry
- Proportion of urban residents at cohort entry
- Socioeconomic status (measured using income quintiles at cohort entry)
- Prescriber of initial prescription:
  - Specialist
    - Haematology
    - Oncology
    - Internal medicine
    - Cardiology
    - Orthopedic surgery
  - General Practitioner
- LMWH drug prescribed
- Number of physician office visits within the last 1 year (median, IQR)
- Number of unique medications used in past 1 year (median, IQR)
- Past hospitalization or ED visit within the last 1 year (median, IQR)
- Measures of Comorbidity
  - Charlson comorbidity score (based on last 3 years of hospitalization data)
- Past medication use (120 days):
  - Warfarin

- NOAC (rivaroxaban, dabigatran, apixaban)
- Aspirin
- Plavix
- Indication for Use
  - Users with DVT
    - Emergency room visit or hospitalization with DVT. Defined as discharge date with DVT ICD-10 codes in 30 days prior to LMWH prescription
  - Users with DVT and past use of warfarin
    - Emergency room visit or hospitalization with DVT. Defined as discharge date with DVT ICD-10 codes in 30 days prior to LMWH prescription and warfarin prescription in 30 days prior to LMWH prescription
  - Users with pulmonary embolism (PE)
    - Emergency room visit or hospitalization with PE. Defined as discharge date with PE ICD-10 codes in 30 days prior to LMWH prescription
  - Pregnant or lactating females
    - Identify pregnant females as those prescribed a LMWH within the 9 months prior to giving birth
    - Identify lactating females as those prescribed a LMWH within 1 year after giving birth
  - Post-operative prophylaxis of venous thromboembolic events in patients undergoing orthopedic surgery of the lower limbs such as hip fracture, hip replacement or knee surgery.
    - Defined as discharge date from hospitalization for a surgery in 30 days prior to LMWH prescription
  - Cancer diagnosis prior to LMWH prescription

#### **Stratification:**

- Limited Use (LU) code on prescription
  - Deep venous thrombosis (DVT) (LU code 186)
  - Pregnant or lactating females (LU code 187)
  - DVT in patients whom treatment with warfarin is not tolerated (LU code 188)
  - DVT in patients who have failed treatment with warfarin (LU code 189)
  - pulmonary embolism (LU code 323)
  - post-operative prophylaxis of venous thromboembolic events in patients undergoing orthopedic surgery of the lower limbs (LU code 378 for LMWH drug fondaparinux only)
  - Other LU code
  - No LU code

#### **Report:**

1. Measures of interest
2. Indication for use by LU code

#### **Limitations:**

- The completion of the LU code in the ODB dataset is unknown. Therefore, individuals with missing LU codes may have had an LU code on their prescription that was not captured in the administrative databases. However, since some of these products are covered through the exceptional access program (EAP), we will assume that if they do not have an LU code it is most likely due to accessing these products through the EAP.
- Codes to define DVT and PE in the administrative databases have not been validated, thus misclassification of indication is possible.

- The definition for new use excludes individuals who had a prescription for a LMWH drug in the past 180 days. Therefore individuals who had an acute episode treated recently will be excluded.
- Information is not available for medication use when hospitalized.
- We will only capture pregnant woman who deliver a live birth in an Ontario Hospital

## **Objective 4b: To Investigate Duration of Publicly-Funded Low Molecular Weight Heparin Use among Newly Initiated Patients in Ontario**

**Study Design:** Cohort study

**Study Period:** January 2002-December 2014

- Accrual Period: January 2002-December 2012
- Maximum follow-up date: December 2014 (*2 year minimum follow-up*)

### **Data Sources:**

- Ontario Drug Benefit Database (ODB)
- Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)
- Canadian Institute for Health Information- National Ambulatory Care Reporting System (CIHI-NACRS)
- Ontario Health Insurance Plan Claims Database (OHIP)
- ICES Physician Database (IPDB)
- Ontario Cancer Registry (OCR)
- Mother-Baby Linked Database (MOMBABY)

**Inclusion Criteria:** All publicly-funded beneficiaries in Ontario who are newly prescribed a low molecular weight heparin

- New users aged 66 and older defined as having no prescription for a LMWH in the past 180 days
- New users  $\leq 65$  years of age defined as having a prescription for any drug in the past 181-365 days and who did not have a prescription for a LMWH in the past 180 days

**Cohort Entry Date:** Date of first prescription for a LMWH over the study period.

**Index Drug:** Defined as the LMWH drug that was prescribed on cohort entry date

**Duration of Treatment:** Define ongoing use of LMWH treatment according to receipt of a subsequent prescription within 1.5 times the day supply (with a minimum 10 day grace period) on the prior prescription. If no subsequent prescription, then person discontinued use.

- Follow individuals forward until first of:
  - Drug discontinuation
  - Death
  - End of study period (December 31, 2014)
  - Max follow-up (2 years)
- Date of discontinuation: date of last prescription + days supply of final prescription

### **Measures of Interest:**

- Number of new users
- Median duration LMWH treatment (based on Kaplan Meier estimates)
- Number of individuals exceeding the LU authorization criteria (1 year)
  - LU notes:

- Max 3 weeks for acute treatment of DVT or PE (LU code 186, 323)
- 9 days of reimbursement for post-surgery (LU code 378)
- Max 1 year for all other indications (LU code 187, 188, 189)

**Stratification:**

- Limited Use (LU) code on prescription
  - Deep venous thrombosis (DVT) (LU code 186)
  - Pregnant or lactating females (LU code 187)
  - DVT in patients whom treatment with warfarin is not tolerated (LU code 188)
  - DVT in patients who have failed treatment with warfarin (LU code 189)
  - pulmonary embolism (LU code 323)
  - post-operative prophylaxis of venous thromboembolic events in patients undergoing orthopedic surgery of the lower limbs (LU code 378 for LMWH drug fondaparinux)
  - Other LU code
  - No LU code

**Limitations:**

- The completion of the LU code in the ODB dataset is unknown. Therefore, individuals with missing LU codes may have had an LU code on their prescription that was not captured in the administrative databases. However, since some of these products are covered through the exceptional access program (EAP), we will assume that if they do not have an LU code it is most likely due to accessing these products through the EAP.
- Codes to define DVT and PE in the administrative databases have not been validated, thus misclassification of indication is possible.
- The definition for new use excludes individuals who had a prescription for a LMWH drug in the past 180 days. Therefore individuals who had an acute episode treated recently will be excluded.
- Information is not available for medication use when hospitalized.
- We will only capture pregnant woman who deliver a live birth in an Ontario Hospital

**Objective 5:****To report the number of accepted submissions for public drug funding for low molecular weight heparins in Ontario**

**Study Design:** Cross sectional study

**Study Period:** Fiscal year 2014

**Data Sources:** EAP LMWH application forms

**Key Variables of Interest:**

- Number of EAP applications for LMWH use
- Number (%) of applications that were approved
- Number by Indications and by drug