ICES Dataset Creation Plan

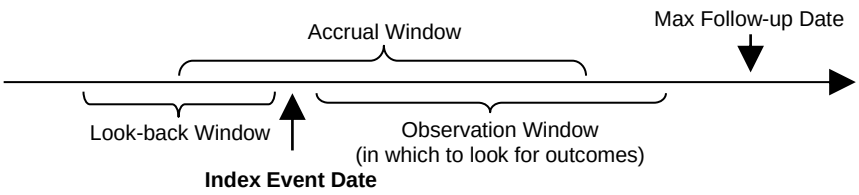
Project Initiation	
Project Title:	***Effectiveness and Safety of Oral Anticoagulants in the Transition Period from Hospital to Home (OAC Post-discharge Events)***
Project Objectives:	Anticoagulants are the leading cause of medication-related serious harm as measured by emergency department visits, hospitalizations and fatalities (1, 2). Each adverse drug event requiring a hospital visit approximately doubles the cost of care in the subsequent 6 months (3). More than 30 million prescriptions per year are dispensed in North America for oral anticoagulants (OACs), which include warfarin, dabigatran, rivaroxaban, apixaban and edoxaban (4-6). The high prevalence of OAC use among older adults, combined with their important clinical benefits in terms of reducing rates of stroke, embolism, and death, and their potential for causing major harm (primarily bleeds, which can be fatal), make them a medication safety priority. In Ontario, the new direct acting anticoagulants (DOACs), while easier to manage than warfarin, have created opportunity for medication errors, given their multiple dosage regimens, bridging requirements, and variable coverage, and have added more than $110 million annually to the public drug plan budget.(7-9) Quality of care in the transition from hospital to home has been identified as a particular problem, with age, number of medications, antithrombotic drugs and poor communications identified as predictors of harm in this period.(10) Although Health Quality Ontario has created a quality standard for transitions of care, their suggestions for improvement are based on opinions regarding helpful interventions rather than data on underlying prevalence of adverse events or effectiveness and safety of interventions.(11) In preparation for a randomized trial of care coordination intervention for oral anticoagulant users being discharged from hospital, this project aims to evaluate the effectiveness and safety of Oral Anticoagulants (OACs), in the early post-hospital discharge period compared to later. **The primary objective is to measure the person-years rate of hemorrhage and thrombotic events in both incident and prevalent users of OACs within the 30 day post-discharge period compared to longer term, that is 30 days to 1 year post-discharge.** Note: Dabigatran, rivaroxaban and apixaban represent the direct acting oral anticoagulants medications and are abbreviated (DOACs). Oral anticoagulants (OAC) refer to both Warfarin and DOACs.

Appendix 1, as supplied by the authors. Appendix to: Holbrook A, Benipal H, Paterson JM, et al. Adverse event rates associated with oral anticoagulant treatment early versus later after hospital discharge in older adults: a retrospective population-based cohort study. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200138.

Principal Investigator (PI):	Dr Anne Holbrook	

Data	
General Use Datasets – Health Services	***Years (where applicable)***
CIHI DAD	2007-2015
NACRS	2007-2015
OHIP	1990-2016
ODB	2009-2016
General Use Datasets – Care Providers	
IPDB	2010-2016
General Use Datasets – Population	
RPDB	1990 –2016
General Use Datasets – Coding/Geography	
DIN	
General Use Datasets - Other	
Ontario Diabetes Database-Registry (ODD)	2007- 2016
Congestive Heart Failure-Registry (CHF)	2007- 2016
Ontario Hypertension Database-Registry (HYPER)	2007-2016
Controlled Use Datasets	
OCR	2009- 2016

Project Cohort	
Study Design	☐ Cross-sectional study ☐ Matched cohort study ☐ Case-control study ☒ Cohort study ☐ Other (specify):



Accrual Start/End Dates	September 1, 2010 to March 31, 2015	
Max Follow-up Date	March 31, 2016	
Inclusion Criteria	Discharge from a hospital (CIHI-DAD, ddate) during accrual window in Ontario for any reason **EXCEPT major bleeds** (defined below) **AND** dispensed an OAC (ODB servdate for warfarin, dabigatran, rivaroxaban and apixaban) within 1 day post-discharge. This includes a prescription on 1) Day prior to discharge 2) day of discharge or 3) day after discharge **Major bleed** defined as any bleed that was the cause of hospitalization, for example intracranial bleed, upper gastrointestinal bleed, lower gastrointestinal bleed or other (**diagnostic codes in Table**)	
Inclusion Criteria Hospitalization Date	**Inclusion Criteria Hospitalization Date:** Date of first hospital discharge (CIHI-DAD ddate) that meets our inclusion criteria in accrual window. Based on date of last **episode** of care (use CIHI-DAD epi variable). **Admission Date**: Date of admission for the hospitalization identified above	
Cohort Entry	Date of first OAC prescription following cohort hospitalization date	
Exclusions (in order)	***Step***	**Description**
	1	Missing ICES Key number (IKN)
	2	Age < 66 at cohort entry
	3	Death prior to cohort entry
	4	Missing sex
	5	No OAC prescription within 1 days of hospitalization date (prescription servdate on hospital discharge date or day after discharge).
	6	Among people who received an OAC prescription prior to discharge, exclude those who received more than one type of OAC on the prescription date closest to cohort entry

Exposure Definition	**<u>OAC Users will be stratified into 3 different groups:</u>** **1. Incident User** • Defined as an individual who received an OAC within the 1 day following hospital discharge and were NOT dispensed an OAC in the 1 year prior to hospital discharge **2. Prevalent User** • Defined as an individual who received an OAC within the 1 day following hospital discharge and were dispensed an OAC in the 1 year prior to hospital discharge • **Among this group, report the number and % who switched therapy:** Look back for the previous OAC prescription prior to hospital admission date. If the previous prescription was for a different OAC, define this user as a **"Prevalent User: Switcher"** **NOTE:** Cohort will not include individuals who were prevalent users prior to hospitalization and discontinued after discharge (no prescription in 1 day following discharge). We are interested in those who initiate therapy immediately after hospitalization to determine the impact of the hospitalization. This will also exclude prevalent users who paused therapy after their hospitalization or who did not fill a prescription following their hospitalization.
Continuous Use of OAC after discharge	From **Cohort Entry Date**, define continuous use of OAC as a subsequent prescription for ANY OAC drug (warfarin or DOAC) within 1.5 times the day supply of the previous OAC prescription PLUS a minimum grace period of 30 days. For example, if someone received a prescription for <20 days supply, look forward 30 days, if someone received a prescription for 20 or more days supply look forward 1.5x the day supply. If a person did not receive a subsequent prescription they discontinued use. Look forward for ANY OAC prescription, not just index drug (ie. Intention to treat analysis, allowing switching between DOAC and warfarin). Do not allow any carry over pills in definition of continuous use. Define **date of discontinuation** as the date of last prescription plus 1.5 times the day supply of the OAC prescription and use a minimum grace period of 30 days. For example, if anyone has <20 day supply on their last prescription, set their date of discontinuation as servdate on last prescription PLUS 30 days (servdate+30).

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When does observation window terminate?	First of: 1. Max follow-up date (March 31, 2016) 2. Death date (RPDB dthdate) 3. Date of OAC discontinuation (defined above) 4. DAD hospitalization for reason outside of our outcomes (defined below) a. Censor individuals who have 5 or more days in hospital (considering entire episode of care) 5. End of Follow-up: 365 days **Note:** Observation window will NOT terminate after the patient's first event, patients will be followed until the observation window terminates and each event will be counted towards the numerator in the rate of event.
Variables	
Checks:	NOTE: We checked how many people had an outcome (bleed or thrombotic event) on the date of discharge, stratified by whether they received their prescription on discharge date or after discharge date. There were no patients who had a bleed on the date of discharge when their first OAC prescription was on the day after discharge. We did find that 10 people who received their OAC prescription on the date of hospital discharge had an ED visit for bleed on the date of discharge that was unrelated to their hospitalization. These people will be counted towards our outcome definition.
Baseline Characteristics	**Demographics:** 1. Age at cohort entry ○ Median (IQR) ○ Age category ▪ 66-75 ▪ 76-85 ▪ 86 and older 2. Sex- N, % male 3. Socioeconomic status (RPDB incquint variable) at cohort entry 4. Urban/rural (RPDB rural variable) at cohort entry 5. OAC dispensed at index prescription date, stratifying variable: ○ Warfarin (druglist Drug= "WARFARIN") ○ Dabigatran (druglist Drug="DABIGATRAN") ○ Rivaroxaban (druglist Drug= "RIVAROXABAN") ○ Apixaban (druglist Drug= "APIXABAN") **<u>Other Variables:</u>**

	6. Physician specialty on or prior to discharge date on hospitalization: o Pull OHIP records (servdate) between cohort hospital admission and discharge date. Keep only one OHIP claim per person, per physician, per day. Get the physician mainspecialty using getipdp macro. Report physician specialty that is closest to discharge date. Group non-mutually exclusive as: ▪ Internal Medicine (yes/no) • Mainspecialty=”INTERNAL MEDICINE” ▪ Hematologist (yes/no) • Mainspecialty=”HEMATOLOGY” OR “HEMATOLOGICAL PATHOLOGY” ▪ Cardiologist (yes/no) • Mainspecialty=”CARDIOLOGY” ▪ Any of the above: Internal Medicine, Hematologist , Cardiologist (yes/no) ▪ NOTE: if no OHIP record during hospitalization, group as ‘unknown’ o 7. Index prescription prescriber specialty: o Get the physician mainspecialty using getipdp macro. Group non-mutually exclusive as: ▪ Internal Medicine (yes/no) • Mainspecialty=”INTERNAL MEDICINE” ▪ Hematologist (yes/no) • Mainspecialty=”HEMATOLOGY” OR “HEMATOLOGICAL PATHOLOGY” ▪ Cardiologist (yes/no) • Mainspecialty=”CARDIOLOGY” ▪ Any of the above: Internal Medicine, Hematologist , Cardiologist (yes/no) 8. Number of distinct OAC drugs dispensed over follow-up o Report Median (IQR)
<u>Indications:</u>	1. Atrial fibrillation diagnosis in the 10 years prior to cohort entry : o Emergency Department (ED) visit (NACRS source=ed, inclsuspect=F, incluscheduled=F, date=regdate) or inpatient hospitalization (CIHI-DAD acute=T, inpatient=T, all dxtype, inclsuspect=F, date=ddate) for atrial fibrillation o ICD9: 4273,42731, 42732 (atrial fibrillation or flutter)

	○ ICD10: I48 codes (I480 (atrial fibrillation), I481 (atrial flutter) 2. Joint replacement using DAD CCI codes in the 35 days prior to cohort entry [INCODE1-20]: ○ Total Hip Anthroplasty: ▪ 1VA53: implantation of internal device, hip joint ○ Total Knee Anthroplasty: ▪ 1VG53: implantation of internal device, knee joint 3. Major surgery during cohort entry hospitalization ○ Use any procedure time>=120 minutes to define major surgery (variable INDUR1-20 > 120 min). ○ Specify intervention location [INLOC1-20] = 01 (main operating room) to only include surgical procedures. 4. Number (%) of patients with active cancer defined as: ○ OCR diagdate in the past 180 days prior to cohort entry **OR** ○ Cancer related surgery in DAD in the past 180 days (use incode variable to look for CCI codes included in appendix) **OR** ○ OHIP feecodes in the past 180 days: ▪ Chemotherapy: G281 G339 G345 G359 G381 G382 G075 G039 G388; ▪ Radiation: X310 X311 X312 X313 X322 X323 X423 X325 X334 X305 X306 Note: Cancer is a uniquely high risk factor for TE events, possibly for bleeding too but less so. Palliative care patients won't have chemo/radiotherapy but might still have active cancer. Cancer is an indication for longer treatment duration 5. Venous thromboembolism (DVT or PE) code during cohort entry hospitalization (diagnostic codes in Table)
<u>Comorbidities:</u>	Macro parameters for ED visits (NACRS): source=ed, inclsuspect=F, incluscheduled=F, date=regdate Macro parameters for inpatient visits (CIHI-DAD): acute=T, inpatient=T, all dxtype, inclsuspect=F, date=ddate Macro parameters for physician visits (OHIP): source=nonlab, spec=medical **<u>Utilization Comorbidities:</u>**

	• Number of distinct non-OAC drugs dispensed in the 365 days preceding cohort entry date. Based on DRUGNAME, do not include drug names listed as anticoagulants.
	  ○ Report Median (IQR)
	• Number (%) of patients dispensed drugs known to interact with oral anticoagulants in the 120 days before cohort entry **(see ICES Druglist). Separate based on anticoagulant potentiation vs anticoagulant inhibition.**
	  ○ Anticoagulants (DCLASS=OAC)
	  ○ Aspirin (DCLASS=antiplatelet and Aspirin=Y)
	  ○ Antiplatelets (excluding aspirin) (DCLASS=antiplatelet and Aspirin=N)
	  ○ NSAIDS (DCLASS="NSAIDS")
	  ○ SSRI (DCLASS="SSRI")
	  ○ Amiodarone (DCLASS="AMIODARONE")
	• Number (%) of patients dispensed drugs known to interact with oral anticoagulants in the 30 days before cohort entry **(see Druglist)**
	  ○ Antibiotics (DCLASS="ANTIBIOTICS")
	• Number of hospitalizations in the past year
	  ○ Using CIHI-DAD: acute=T, inpatient=T, all dxtype, inclsuspect=F, date=ddate
	  ○ Report median (IQR)
	• Charlson Score based on 3 year of hospitalization data prior to cohort entry:
	  ○ Categorize as "No hospitalization" (for those with no hospitalization), 0, 1, 2+
	
	• Admission to a hospital or emergency department for a **<u>thrombotic event</u>** in the past 3 years from cohort entry **(Diagnostic codes in Table).**
	  ○ Ischemic Stroke
	  ○ Transient Ischemic Stroke (TIA)
	  ○ Peripheral Vascular disease:
	  ○ Venous thromboembolism:
	  ▪ Deep vein thrombosis
	  ▪ Pulmonary embolism
	  ○ Systemic embolism
	
	• Admissions to hospital or emergency department for **<u>hemorrhag</u>**e in the past 3 years from index date. **(Diagnostic codes in Table)**
	  ○ Intracranial Bleeding

	○ Upper Gastro intestinal Bleeding ○ Lower Gastrointestinal Bleeding ○ Other Major bleeds • Diseases and medical conditions that predicts thrombotic events or hemorrhage in **3 years prior to index date**: ○ **CHADS-VASC score components** ▪ Congestive heart failure (CHF database): 1 point ▪ Hypertension (HYPER database, diagdate<index date) : 1 point ▪ Age 75 yr or older: 2 points ▪ Diabetes Mellitus (ODD database, diagdate<index date): 1 point ▪ Previous thromboembolism (ischemic stroke, transient ischemic attack (TIA), peripheral artery embolism or pulmonary embolism): Any or more than 1 of these codes leads to 2 points. Total score can be 0 or 2. ▪ Vascular disease: 1 point ▪ Age 65-74 years: 1 point ▪ Female Sex: 1 point ○ **CHADS-VASC score (mean)** ▪ Mean Score (SD) ▪ Median Score (IQR) ▪ Score (0 to 9) ○ **HasBled score components** (**Diagnostic codes Appendix 5**) ▪ Hypertension (HYPER database, diagdate<index date): 1 point ▪ Abnormal renal function: 1 point ▪ Abnormal liver function: 1 point ▪ Stroke or TIA: 1 point ▪ Bleeding history: 1 point ▪ Elderly: Age over 65: 1 point ▪ Drug consumption or alcohol abuse: 1 point if drug consumption and 1 point if alcohol abuse. Total score can be 0, 1 or 2 • Drug consumption: treatment with platelet inhibitors(DCLASS=antiplatelet) or NSAIDs (DCLASS=NSAID) overlapping index OAC prescription • Alcohol abuse: see codes

	▪ NOTE: We are unable to obtain one component: L - Labile INR or TTR. ○ **HasBled score (mean)** ▪ Mean Score (SD) ▪ Median Score (IQR) ▪ Score (0 to 9)
Stratifications	1. Type of User (defined in exposure groups above) 2. Type of OAC dispensed on index date (if feasible) ○ DOAC vs. warfarin
Outcomes	
Primary Outcome Definition	Rate of hospitalizations or ED visits for OAC adverse events per 100 person-years, defined as: 1. Major hemorrhage 2. Thrombotic event **<u>Outcome Definitions:</u>** ***Only keep one record for each episode of care for a patient. Exclude NACRS records with to_type='S' or 'I'*** Macro parameters for ED visits: source=ed, inclsuspect=F, incluscheduled=F, date=regdate Macro parameters for inpatient (DAD) visits: acute=T, inpatient=T, all dxtype, inclsuspect=F, date=ddate **1. <u>Any major Hemorrhage: (</u>Table)** Definition: Symptomatic bleeding in a critical area or organ requiring admission to hospital or visit to emergency department. One of the following: a. Intracranial Bleeding b. Upper Gastro intestinal Bleeding c. Lower Gastrointestinal Bleeding d. Other Major bleeds **2. <u>Thrombotic Event</u>** Definition: Pathology characterized by the formation of a blood clot that occludes and obstructs blood flow through the circulatory system. One of the following: a. Ischemic Stroke b. Transient Ischemic Stroke (TIA) c. Peripheral Vascular disease embolism or emergency rescue procedure d. Venous thromboembolism: i. Deep vein thrombosis ii. Pulmonary embolism

	e. Systemic embolism Codes to determine these events are shown in the Table. **For each outcome report:** **1. Number of events during 1 year of follow-up** **2. Overall rate of events calculated as** a. Numerator: number of events that occurred within 0-365 days of cohort entry b. Denominator: person-years within 365 days of cohort entry. Person years calculated as the sum of the days between cohort entry and end of window observation termination for each person. c. Report rate as numerator/denominator*100 and 95% Confidence Intervals **3. 30 day rate calculated as:** a. Numerator: number of events that occurred within 30 days of cohort entry b. Denominator: person-years within 30 days of cohort entry. Person years calculated as the sum of the days between cohort entry and end of window observation termination for each person or 30 days, whichever occurs first. c. Report rate as numerator/denominator*100 and 95% Confidence Intervals **4. 31-365 day rate calculated as:** a. Numerator: number events that occurred between 31 days after cohort entry to 365 days after cohort entry b. Denominator: person-years between 31 days after cohort entry to 365 days after cohort entry. Person years calculated as the sum of the days between 31 days after cohort entry and the end of window observation termination for each person. Note if someone's observation window terminates before 31 days, they are not included. **c.** Report rate as numerator/denominator*100 and 95% Confidence Intervals **For each outcome (major hemorrhage or thrombotic event) report:** **1. For each 30 day increment after cohort entry report:** a. Number of events that occurred in the 30 day increment b. Number of individuals still in follow-up during 30 day increment c. Event rate per 100 person years

	i. Numerator: number of events that occurred in the 30 day increment ii. Denominator: person-years in the 30 day increment. Person years calculated as the sum of the days between start of 30 day increment and the end of either the window observation termination for each person or end of 30 day increment for each person, whichever occurs first. iii. Report rate as numerator/denominator*100 and 95% Confidence Intervals
Stratifications	1. Type of outcome 2. Type of User (defined in exposure groups above) 3. Type of OAC dispensed on index date (if feasible) o DOAC vs. warfarin 4. Gender

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Table: Diagnosis and Procedure codes for Outcomes

Event Type	**ICD-10 Diagnostic Codes†**	**Procedure Codes (CCI and CCP)†**
Thromboembolic Events		
Deep Vein Thrombosis	I80.1, I80.2, I80.3, I80.8, I80.9, I82	
Pulmonary Embolism	I26	
Ischemic Stroke	I63, I64, H34.1, H34.2, H34.8, H34.9	
Transient Ischemic Attack	H34.0, G45.0, G45.1, G45.2, G45.3, G45.8, G45.9	
Peripheral Vascular Disease or Emergency Rescue Procedure	I70, I73.1, I73.8, I73.9, K55.1	CCI= 1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76, 1KG87, 1IA87, 1IB87, 1IC87, 1ID87, 1KA87, 1KE57 CCP= 5125, 5129, 5014, 5016, 5018, 5028, 5038, 5126, 5159
Systemic Embolism	I74	
Additional ThromboembolicEvent Codes (Sensitivity Analysis)		
Myocardial Infraction	I21, I22, I23	
Coronary Artery Bypass Grafting	Z95.1	CCI= 1IJ76 CCP= 481, 4811, 4812, 4813, 4814, 4815, 4816, 4817, 4819
Percutaneous Coronary Intervention		CCI= 1IJ50, 1IJ57 CCP= 4802, 4803, 4809
Hemorrhage		
Intracerebral	I60, I61, I62, S06.4, S06.5, S06.6	
Upper Gastrointestinal	I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4,	

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	K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80, K63.80, K92.0, K92.1, K92.2	
Lower Gastrointestinal	K55.20, K62.5	
Other	N02, K66.1, N93.8, N93.9, N95.0, R04, R31, R58, D68.3, H35.6, H43.1, H45.0, M25.0, J94.2, T79.2, N42.1, H11.3, H31.3, J950.0	

† ICD-10 - International Classification of Diseases, Tenth Revision; CCI - Canadian Classification of Healthcare Interventions Codes; CCP - Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures