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Predictors of Oral Anticoagulant-associated Adverse Events in Seniors Transitioning from Hospital to Home: A Retrospective Cohort Study Protocol

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TITLE: Predictors of Oral Anticoagulant-associated Adverse Events in Seniors Transitioning from Hospital to Home: A Retrospective Cohort Study Protocol

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ABSTRACT:

Introduction

Oral anticoagulants (OACs) are widely prescribed in older adults. High OAC-related adverse event rates in the early period following hospital discharge argue for an analysis to identify predictors. Our objective is to identify and validate clinical and continuity of care variables amongst seniors discharged from hospital on an OAC, which are independently associated with OAC-related adverse events within 30 days.

Methods and Analysis

We propose a population-based retrospective cohort study of all adults aged 66 years or older who were discharged from hospital on an oral anticoagulant from September 2010 to March 2015 in Ontario, Canada. The primary outcome is a composite of the first hospitalization or Emergency Department visit for a hemorrhage or thromboembolic event or mortality within 30 days of hospital discharge. A Cox proportional hazards model will be used to determine the association between the composite outcome and a set of prespecified covariates. A split sample method will be adopted to validate the variables associated with OAC-related adverse events.

Ethics and Dissemination

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. Results will be disseminated via peer-reviewed publications and presentations at conferences and will determine intervention targets to improve OAC management in upcoming randomized trials.

ARTICLE SUMMARY:

Strengths and Limitations

- Few studies have examined factors that predict medication safety adverse events during periods of transitions of care.
- In this large, population-based cohort study of seniors, we examine both clinical and continuity of care risk factors for oral anticoagulant (OAC)- related adverse events post-hospitalization.
- This study is subject to the limitations inherent in observational design and the use of health administrative databases.

INTRODUCTION

Background/Rationale

Oral anticoagulants (OACs) are commonly prescribed for the prevention and treatment of stroke, systemic embolism and venous events associated with atrial fibrillation (AF) and venous thromboembolism (VTE) [1-3]. Despite the introduction of direct-acting oral anticoagulants (DOACs), which do not require routine laboratory monitoring and are associated with less bleeding than warfarin, OACs remain a top cause of serious drug-related harm, primarily bleeding and thromboembolic events [4,5].

It is estimated that between 2013 and 2014 OACs were implicated in 28% (95% confidence interval [CI)] 23-32%) and 39% (95% CI 33.7-43.8%) of emergency department (ED) visits in the United States for adverse drug events among adults aged 65 to 79 years and those 80 years or older, respectively [6]. In Canada, it is estimated that OACs account for 12.6% of adverse drug reaction-related hospitalizations among seniors between 2006 and 2011 [7].

Observational studies using population-level data report even higher adverse event rates for OAC users during periods of transitions in care, specifically during the early post-hospitalization period. Amongst the elderly, a bleeding risk of 26.4% (95% confidence interval [CI] 25.3-27.4) per person-year, and a thromboembolic event risk of 32.4% (95% CI 31.3-33.5) per person-year, were identified in OAC users within the first 30-days after hospital discharge [8].

The high rates of adverse events in the early post-discharge period suggest that continuity of care during this hectic time for patients transitioning out of the hospital may be part of the problem [9,10]. Continuity of care is defined by the World Health Organization as "the degree to which discrete health care events are experienced by people as coherent and interconnected over time and consistent with their health needs and preferences" [11]. Several studies have found that prompt primary care follow-up of patients after hospital discharge reduces subsequent ED visits and hospitalizations among patients with chronic conditions such as congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction and cancer [12-18]. Many clinical practice guidelines recommend physician follow-up within 1-2-weeks post-discharge as best practice to improve continuity of care [10,19-24].

Coordinating medication management post-hospitalization is challenging, with adverse drug events reported as among the most common reason for post-discharge readmission and ED visits [25-27]. Poor medication management immediately following hospital discharge has been reported to increase the risk of 30-day readmission by 28% [28].

In order to improve the management of OAC therapy in the senior population post-discharge, this study aims to identify important risk factors, both clinical and continuity of care, predicting OAC-related harm in the short-term period following hospitalization. Validated process of care risk factors may be useful targets for future intervention trials.

Objectives

Research Question: Among Ontario residents aged 66 years or older who were discharged from hospital on an OAC (warfarin, dabigatran, rivaroxaban, or apixaban), which clinical and continuity of care variables are significantly associated with time to re-hospitalization or an emergency department visit for a hemorrhage or thromboembolic event, or mortality within 30 days post-discharge?

Hypothesis: In addition to traditional clinical risk factors for OAC-related adverse events, factors related to continuity of care, particularly contact with a primary care physician, nurse practitioner, medical specialist or home care services within 7 days of discharge, will be associated with lower risk for the composite outcome in the 30 days following hospitalization.

METHODS AND ANALYSIS

Reporting will be compliant with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Study Design

We will use a population-based retrospective cohort study to identify potential patient, provider, and institution-level factors and continuity of care factors independently associated with OAC-related adverse events in seniors using routinely collected administrative health data. These data are more accurate than self-reported data and minimize selection bias [29,30].

Setting

Our study will be set in Ontario, Canada. Ontario is Canada's most populous province, with over 14 million residents in 2018, representing about 39% of the country's population [31].

Data Sources

The study dataset will be created using the province of Ontario's health administrative databases housed at ICES. These databases contain administrative health service records for the approximately 14 million Ontarians eligible for health coverage [32-36]. These databases are linked using encrypted patient-specific identifiers. Table 1 summarizes the database names and contents of those that will be used to create the study dataset.

Table 1: Description of ICES Databases

Name of Database	Content of Database
Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	Patient-level demographic, diagnostic, procedural and treatment information on all acute care hospitalizations
CIHI—National Ambulatory Care Reporting System (CIHI-NACRS)	Patient-level demographic, diagnostic, procedural and treatment information for all hospital-based and community-based ambulatory care
Client Agency Program Enrollment Database (CAPE)	Information regarding enrollment of individuals with primary care practitioners, teams and networks
ICES-Derived Cohorts	Validated cohorts of individuals with specific diseases and conditions. These include: the Ontario Congestive Heart Failure (CHF) Database [37]; Ontario Dementia Database (DEMENTIA) [38]; Ontario Diabetes Database (ODD) [39]; Ontario Hypertension Dataset (HYPER) [40,41]

ICES Physician Database (IPDB)	Characteristics of physicians and surgeons licenced to practice in Ontario
Ontario Cancer Registry (OCR)	Patient-level demographic, cancer diagnosis and cancer-related mortality information
Ontario Continuing Care Reporting System (CCRS)	Demographic, clinical, functional and resource utilization information on individuals receiving hospital-based complex continuing care services
Ontario Drug Benefit Program Database (ODB)	Records of dispensed outpatient prescriptions paid for by the provincial government
Ontario Health Insurance Plan Claims History Database (OHIP)	Claims for physician services paid for by the provincial government
Ontario Health Insurance Plan Registered Persons Database (RPDB)	Demographic, place of residence and vital status information for all persons eligible to receive insured heath services in the province
Ontario Home Care Database (HCD)	Patient-level demographic, diagnostic, procedural and treatment information on all home care visits
Ontario Mental Health Reporting System Database (OMHRS)	Patient-level demographic, diagnostic, procedural and treatment information on all adult inpatient mental health visits
Ontario Ministry of Health and Long-Term Care Institution Information System	Ontario health care institution information
Resident Assessment Instrument—Contact Assessment (RAI-CA)	Patient-level demographics, diagnosis and treatment information used to guide intake of patients into home care services
Resident Assessment Instrument—Home Care (RAI-HC)	Contains data that assesses the care and needs of adult patients in hospital and community settings for in-home and placement services
Statistics Canada Census Postal Code Conversion File	Information on rural residence and income quintiles of residents

Observation Period

We define the study's index date as the date of OAC dispensing, which had to be within one day of hospital discharge. The patient accrual period will be September 1, 2010 through March 31, 2015. This period captures the time following the approval of DOACs by Health Canada and allows for a sufficient sample size to conduct this study [42].

We will define a 7-day post-discharge blanking period during which patients will have been dispensed an index OAC, but study outcome events will not be measured. All patients who died or experienced a hospitalization or an ED visit for a thromboembolic or hemorrhagic event within the 7-day blanking period will be excluded. For those who remain in the cohort, health care contacts during the blanking period will be recorded.

Patients will be followed from the end of the blanking period (Day 8) until day 30 post-hospitalization (or a maximum follow-up of 24 days), with the last outcome event date being 30 April 2015. We will assume that all patients continuously use OACs during follow-up. However, patients will be censored at a hospitalization lasting more than 5 days, as information on in-hospital

medications are not available in administrative claims data and medications are often changed or discontinued during hospital admission [43,44].

Participants

Inclusion and Exclusion Criteria

The source population will be all Ontario residents aged 66 years or older who are discharged from an acute care hospital and dispensed a single OAC - warfarin, dabigatran, apixaban or rivaroxaban at any dose, within one day of discharge. Patients with a most responsible discharge diagnosis of major bleeding, defined as any bleeding event that was the cause for the hospitalization or contributed to the greatest fraction of the length of stay, will be excluded [45]. We will use the Ontario Health Insurance Plan (OHIP) Registered Persons Database (RPDB), which contains insurance coverage, demographic, place of residence and vital status information, together with the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), to identify the study patients. We will also access the prescription drug claims history of eligible patients via the Ontario Drug Benefit Plan Database (ODB). These datasets are linked using unique coded identifiers and will be analyzed at ICES (www.ices.on.ca).

Adults younger than 66 years of age will be excluded to avoid incomplete or missing prescription drug data [46].

Variables

Outcomes

The primary outcome will be a composite of hospitalization or ED visit for a hemorrhage or thromboembolic event, or death from any cause. These events are standard in pivotal trials and are the main OAC-associated serious adverse events. Including death also avoids the problem of competing risks [47-51].

Thromboembolic events will include venous thromboembolic events (deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (ischemic stroke or transient ischemic attack, peripheral vascular disease or emergency rescue procedure, or systemic embolism). The International Classification of Diseases (ICD) 10th revision diagnosis codes, and the Canadian Classification of Health Interventions procedure codes for these conditions are provided in Table 2. Validation studies have found equivalent ICD 9 diagnosis codes to have 91% sensitivity and 95% specificity [52-56]. Hemorrhagic events will include intracranial bleeds, upper and lower gastrointestinal bleeds, and any other bleed which required a hospital admission or a visit to an ED. Table 3 lists the ICD 10 diagnosis codes used to define hemorrhage. Validation studies found equivalent ICD 9 diagnosis codes to have 94% sensitivity and 83% specificity for major hemorrhagic events [54].

Table 2: Diagnosis and Procedure codes used to define thromboembolic outcomes

Thromboembolic Event Type	ICD10 Codes	Canadian Classification of Healthcare Interventions Codes
Deep Vein Thrombosis	I82.8, I82.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.0, I82.1, I82.2, I82.3	
Pulmonary Embolism	I26.0, I26.9	

Ischemic Stroke	I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, 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	I70.0, I70.1, I70.20, I70.21, I70.8, I70.9, I73.1, I73.8, I73.9, K55.1	1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76, 1KG87, 1IA87, 1IB87, 1IC87, 1ID87, 1KA87, 1KE57
Systemic Embolism	I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9	

Table 3: Diagnosis codes used to define hemorrhage outcomes

Hemorrhage Type	**ICD10 Codes**
Intracerebral	I60, I61, I62.0, I62.1, I62.9, S06.400, S06.401, S06.410, S06.411, S06.420, S06.421, S06.430, S06.431, S06.440, S06.441, S06.490, S06.491, S06.500, S06.501, S06.510, S06.511, S06.520, S06.521, S06.530, S06.531, S06.540, S06.541, S06.590, S06.591, S06.600, S06.601, S06.610, S06.611, S06.620, S06.621, S06.630, S06.631, S06.640, S06.641, S06.690, S06.691
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, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K63.80, K31.80, K92.0, K92.1, K92.2
Lower Gastrointestinal	K55.20, K62.5
Other	N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, K66.1, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R31.0, R31.1, R31.8, R58, D68.3, H35.6, H43.1, H45.0, M25.0

The outcomes will be ascertained using CIHI-DAD, CIHI-NACRS and RPDB [57,58].

Risk Factors

Table 4 summarizes the clinical and continuity of care risk factors being explored in this project, as well as their data sources. Patient demographic characteristics captured as of the date of cohort entry will include age, sex, socioeconomic status (as defined by census neighborhood income quintiles), rural residence, and whether the patient is rostered with a primary care physician. In addition, palliative patients will also be identified using a previously validated combination of codes in health administrative databases [37].

Table 4: Clinical and Continuity of Care variables and data sources

Variable	Data Source
Patient Characteristics	
Age	RPDB
Sex	
Income Quintile	Statistics Canada Census Postal Code Conversion File
Rural Residence	
Rostering – patient enrolled in a primary care organization, team or with a primary care physician	CAPE
Palliative Patient – lookback window of 6 months	OHIP, CIHI-DAD, CIHI-NACRS, RAI-CA, RAI-HC, HCD, CCRS
Characteristics of Index Hospitalization	
Type of hospital- Teaching, Community, Small	Ontario Ministry of Health and Long-Term Care
Length of index hospitalization	CIHI-DAD
Specialty of the physician responsible for index OAC prescription- General/Family Practitioner; Cardiology; Hematology; Internal Medicine; Orthopedic Surgery; Oncology; Other Surgery; Other	IPDB
Type of OAC dispensed at index prescription date- Warfarin, Apixaban, Dabigatran, Rivaroxaban	ODB
Type of discharge – Home; Long term or Continuing care facility; Other	CIHI-DAD
Type of OAC User	
Incident-patients who were not dispensed an OAC in the year prior to cohort entry	ODB
Prevalent	
Non-switchers- patients who were dispensed the same OAC in the year prior to cohort entry	
Switchers- patients who were dispensed a different OAC in the year prior to cohort entry	
Comorbidities	
Components of CHA2DS2-VASc* (Not including those mentioned above) – looking at the presence of these medical conditions in the 3 years prior to cohort entry	
Congestive Heart Failure	CHF
Hypertension	HYPER
Diabetes Mellitus	ODD
Prior stroke/ Transient Ischemic Stroke	CIHI-DAD
Peripheral Vascular Disease	
Components of HAS-BLED** (Not including those mentioned above) – looking at the presence of these medical conditions in the 3 years prior to cohort entry	
Abnormal renal/liver function	CIHI-DAD, OHIP
Prior bleeding	CIHI-DAD
Drugs/alcohol concomitantly	CIHI-DAD, ODB

Charlson Comorbidity Score	CIHI-DAD
Other comorbidities	
Dementia	DEMENTIA
Delirium	CIHI-DAD, OMHRS
Diagnosis of obesity in the 3 years prior to cohort entry	CIHI-DAD, OHIP
Diagnosis of underweight in the 3 years prior to cohort entry	
Antiphospholipid syndrome in the 3 years prior to cohort entry	CIHI-DAD
Active cancer	OCR, OHIP
Thromboembolic event	CIHI-DAD, CIHI-NACRS
Substance Abuse	CIHI-DAD, OMHRS, OHIP
Alcoholic Abuse	
Number of hospitalizations in the past year	CIHI-DAD
Recent Anticoagulant use (120 d)	ODB
Indications	
Atrial fibrillation	CIHI-DAD, CIHI-NACRS, OHIP
Joint replacement	CIHI-DAD
Major surgery	CIHI-DAD
Deep vein thrombosis or Pulmonary Embolism	CIHI-DAD, CIHI-NACRS
Mechanical heart valve	CIHI-DAD
Potential Drug Interactions- dispensed in the past 120 days prior to cohort entry, unless otherwise specified	
Non-Steroidal Anti-Inflammatory Drugs***	ODB
Selective Serotonin Reuptake Inhibitors	
Amiodarone	
Aspirin***	
Antiplatelets	
Antibiotics, dispensed in the past 30 days prior to cohort entry	
Number of drugs dispensed which potentially interact with OACs	
Continuity of Care- Health care contact within 7 days of discharge from index hospitalization	
Follow up with primary care physician, nurse practitioner, medical specialist or home care services	OHIP, HCD
Follow up with familiar hospital physician	OHIP
Follow up with familiar community physician	OHIP

Data Sources: RPDB- Ontario Health Insurance Plan Registered Persons Database; CAPE- Client Agency Program Enrollment Database; OHIP- Ontario Health Insurance Plan Claims History Database; CIHI-DAD - Canadian Institute for Health Information–Discharge Abstract Database; CIHI-NACRS - CIHI—National Ambulatory Care Reporting System; RAI-CA - Resident Assessment Instrument—Contact Assessment; RAI-HC - Resident Assessment Instrument—Home Care; HCD- Ontario Home Care Database; CCRS- Ontario Continuing Care Reporting System; IPDB- ICES Physician Database; ODB- Ontario Drug Benefit Program Database; CHF- Congestive Heart Failure database; HYPER- Ontario Hypertension Dataset (HYPER); ODD- Ontario Diabetes Database; DEMENTIA- Ontario Dementia Database; OMHRS- Ontario Mental Health Reporting System Database; OCR- Ontario Cancer Registry; HCD- Ontario Home Care Database.

**CHA2DS2-VASc- Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category.*
***HAS-BLED- Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (excluded), Elderly (>65 years), Drugs/alcohol concomitantly.*
**** Over-the-counter use of drug is not captured.*

Characteristics of the index hospitalization including type of hospital, length of index hospitalization and type of discharge will be captured. We will also capture specialty of the physician responsible for index OAC prescription and OAC dispensed at index prescription date. The cohort will be categorized into three categories of OAC users including incident, prevalent non-switchers and prevalent switchers.

Existing comorbidities may be associated with outcomes [38-40]; therefore, comorbidities including dementia and diabetes will be captured [33,34]. In addition, patients with a history of substance or alcohol abuse in the past 3 years prior to cohort entry will be identified [41]. A diagnosis of obesity, underweight, antiphospholipid syndrome, and delirium will also be captured. Patients with active cancer, defined as individuals who received a cancer diagnosis, cancer related surgery, chemotherapy or radiation in the past 180 days, will be identified. Hospitalization or ED visits in the 3 years prior to cohort entry for thromboembolic or hemorrhagic events will also be recorded.

Several indices, including the Deyo-Charlson Comorbidity Index, a general comorbidity measure developed to predict mortality, also will be calculated to describe the cohort [59]. Validated clinical scores used to guide anticoagulation of patients including the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category) risk stratification scheme for predicting thromboembolism in patients with atrial fibrillation will be calculated [60]. Additionally, the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly) score which was developed to support clinical decision-making regarding anticoagulant therapy in AF patients by predicting bleeding risk in these patients will be calculated [61]. Since data on labile international normalized ratio is not available this will not be calculated as part of the score.

Indications that result in the prescription of OACs will also be recorded to control for confounding by indication including presence of AF in the 10 years prior to cohort entry, joint replacement (hip or knee arthroplasty) in the 35 days prior to cohort entry, major surgery lasting 120 minutes or longer (excluding same day surgery) during index hospitalization, presence of a mechanical heart valve, and deep vein thrombosis or pulmonary embolism during index hospitalization [62-64]. These indications will be inferred from corresponding diagnosis and procedure information, as indications for prescriptions are not recorded in Ontario prescription drug claims.

We will be adjusting for the presence of drug therapies hypothesized to influence the risk of our outcome through potential interactions with OACs by including use of prescription nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), amiodarone, prescription aspirin, and antiplatelets use in the 120 days prior to cohort entry and antibiotic use in the 30 days prior to cohort entry [64-66]. Recent pre-hospital anticoagulant use was also captured.

Continuity of care will be operationalized to measure whether follow-up was performed by a primary care physician, nurse practitioner, medical specialist, or home care services within 7 days of discharge. This measure will help gauge how well outpatient care is coordinated with

hospital care as this is an important aspect of care coordination which may help reduce hospital readmissions [67,68]. In addition, we will capture whether patients had a follow up visit within 1-week post-discharge with any physician with whom they had had at least 2 visits in the 12 months preceding the index hospitalization (community physician) or at least 1 visit during the hospital stay (hospital physician) [10]. Research studies have reported that seeing a physician who is familiar with the patient's health post-hospitalization may have a beneficial impact on follow-up rates and reduce risk of death or readmissions [69].

Quality checks, missing data and extreme values

Data are unlikely to be missing at random [46,58,70]. For categorical variables an additional 'missing' category will be included. If ≥ 10% of observations are missing multiple imputations are planned.

Bias

Bias in pharmacoepidemiology studies results from multiple sources of confounding [67,71,72]. DOAC users tend to be younger with fewer comorbidities than warfarin users [73]. To control for confounding, we will include variables such as age, sex, presence of specific comorbidities, concomitant medications, remote residence, neighbourhood income quintile, and physician specialty amongst other independent variables in the model as potential risk factors.

Given that continuity of care risk factors are hypothesized to be important in the early period after hospital discharge for OAC-related adverse events, the outcome observation period will begin after 7-days post-discharge to avoid survivor-treatment bias [74]. We will report the number patients excluded due to the occurrence of an event during the blanking period.

Sample Size

For Cox regression, a fitted model is likely to be reliable and stable when the number of participants with the outcome (ie, either first hospitalization or ED visit during follow-up for a hemorrhage or arterial or venous thromboembolic event, or death) is 20 times the number of covariates [75]. We anticipate that up to 30 covariates will be included in the Cox regression model; therefore, a minimum of 600 patients with at least one of the outcomes that form the composite will be required to devise the models in this cohort. This is feasible as a similar study reported haemorrhage and thromboembolic event rates of about 26 and 34 per 100 person-years in the first 30 days post-discharge, respectively in a cohort of 123,140 patients [8]. In addition, the long accrual period will also help ensure a sufficient sample size.

Statistical Plan

All data will be examined using descriptive statistics. Categorical variables will be summarized using frequency and percentage. Continuous variables will be summarized using mean and standard deviation (SD) or median and interquartile range (IQR), when results are skewed. Person-time of follow-up will also be captured.

A summary of all planned analysis is provided in Table 5. Given that the primary outcome is a time-to-event outcome, Cox proportional hazards model will be used to determine the association between the composite outcome and all risk factors including patient demographic, index hospitalization descriptors, comorbidity, drug indications, potential drug interactions and continuity of care variables within one-month of hospital discharge.

Table 5: Statistical Plan Summary

Objective/Analyses	**Outcome**		**Method of Analysis**	**Independent Variables**
Primary Objective	Definition	Type		
To determine which clinical and continuity of care variables predict the outcome in senior OAC users post-hospitalization	Re-hospitalization or ED visit for a hemorrhagic or thromboembolic event or mortality in 30-days	Time to event	Cox Proportional Hazards Model	*Demographic* • Income quintile • Rural residence • Patients enrolled under a primary care physician or organization • Palliative Patient *Index Hospitalization Characteristics* • Type of hospital • Specialty of OAC prescribing physician • Type of OAC dispensed • Type of discharge *Type of OAC user* • Incident • Prevalent Non-switcher • Prevalent Switcher *Comorbidities* • CHA2DS2-VASc* • HASBLED** • Dementia • Delirium • Obesity • Underweight • Antiphospholipid syndrome • Active cancer • Prior thromboembolic or hemorrhagic event • Substance abuse • Alcohol abuse • Hospitalization in past year
Sensitivity Analyses				
Include myocardial infarction in the definition of thromboembolic event outcome	Re-hospitalization or ED visit for a hemorrhagic or thromboembolic event or mortality in 30-days	Time to event	Cox Proportional Hazards Model	
Competing Risk Analysis	Re-hospitalization or ED visit for a hemorrhagic or thromboembolic event in 30-days	Time to event	Cause-specific Cox proportional hazards model	
Validation				
Internal validation of the primary model	Re-hospitalization or ED visit for a hemorrhagic or thromboembolic event or mortality in 30-days	Time to event	Split-Sample Method	

				• Recent anticoagulant use Indications • Atrial Fibrillation • Joint replacement • Major surgery • Mechanical heart valve • Deep vein thrombosis or Pulmonary embolism *Potential Drug Interactions* • NSAIDs*** • SSRIs • Amiodarone • Aspirin*** • Antiplatelets • Antibiotics • Number of drugs, potentially drugs interacting with OACs, dispensed *Continuity of Care* • Follow up with primary care physician, nurse practitioner, medical specialist or home care services within 7 days of discharge from index hospitalization

**CHA2DS2-VASc- Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category.*

***HAS-BLED- Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (excluded), Elderly (>65 years), Drugs/alcohol concomitantly.*

**** Over-the-counter use of drug is not captured.*

Model Construction

Model derivation and validation will be based on a split-sample method [76]. Two-thirds of the study participants will be randomly assigned to a model derivation cohort, and one-third will be reserved as an independent validation cohort [77]. Both cohorts will be compared with respect to clinical and continuity of care variables.

The model will be developed based on data from the derivation cohort alone. For the primary outcome, because predictors that are highly correlated with others contribute little independent information, pruning candidate predictors will be required [78]. The effect of multicollinearity between predictors would inflate the variance of the coefficient estimates and makes the estimates very sensitive to minor changes in the model. To avoid this, multicollinearity amongst the covariates will be explored using tolerance statistics and variance inflation factor. Tolerance statistic of below 0.1 and a variance inflation factor of above 10 will indicate multicollinearity. Of the highly correlated independent variables one will be removed from the model based on clinical judgement.

Subsequently, univariate Cox regression models will be used to select variables for entry into the multivariable regression model. If the p-value of a variable is less than or equal to 0.20 that variable will be included in the model building stage of the final multivariate regression model.

To investigate whether significant covariates can modify the effect of other predictors in the Cox proportional hazards model, two-way interactions between clinically significant predictors will be tested. Significant interactions with a p-value of ≤0.05 will be retained and added into the prediction model.

Finally, since this is an exploratory analysis, a backward stepwise approach will be employed for selection of risk factors for inclusion in the final multivariate Cox model [79]. Least significant independent variables including confounding variables will be removed until all p-values are below 0.2. The continuity of care variable, hypothesized to significantly impact the survival of the patient, will be retained in the model. Risk factors with the effects from the Cox proportional hazard's model expressed as the HR, corresponding 95% CI and the associated *p*-value will be reported. The proportionality assumption will be assessed using Schonfeld residuals and interaction of risk factors with time [80]. If proportionality assumption is not met results will be stratified if appropriate. All violations of the proportionality assumption will be reported.

Sensitivity Analysis

There is much debate on effect of oral anticoagulants on acute myocardial infarction. Meta-analyses of RCTs have concluded that the use of dabigatran is associated with an increased risk of acute myocardial infarction [81,82]. Given the evidence on risk for acute myocardial infarction in dabigatran users, a sensitivity analysis with this event in the definition of the composite outcome will be performed using the aforementioned methods.

Moreover, a competing risk analysis is planned where all-cause mortality will be treated as a competing risk for hemorrhagic and thromboembolic events. A cause-specific Cox proportional hazards model will be constructed [83]. Predictors and their coefficients in the cause-specific hazard models will be compared with those in the full Cox model.

Model Validation

Once the final model is developed, it will be assessed in the separate validation cohort of patients. The predictive accuracy of the model will be assessed using tests for discrimination and calibration [80]. We will evaluate the model calibration by conducting the Gronnesby and Borgan

Test which uses martingale residuals to compare the count of events to the semi-parametric estimates from the Cox proportional hazards model on a cumulative hazards scale [80]. Discrimination will be evaluated using Harell's C-index representing the area under the receiver operating characteristic curve with larger values indicating better discrimination [80].

Data management and analysis will be performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient and Public Involvement

The publicly funded research program that includes this study has several patient co-investigators and advisors. Input from 19 patients participating in focus groups on barriers and facilitators for optimal oral anticoagulant management, provided suggestions for predictors. Patients did not contribute to the actual writing or editing of this document.

ETHICS AND DISSEMINATION

All study data reside and are analyzed at ICES (www.ices.on.ca). ICES is a prescribed entity under Section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45, and was approved by ICES' Privacy and Legal Office.

The results of this study will be published in a peer-reviewed journal and presented at national and international conferences. They will also help determine intervention targets to improve OAC management in upcoming randomized trials.

AUTHOR CONTRIBUTIONS:

AH obtained the funding and developed the study idea. HB and AH designed the study. HB obtained data permissions and research ethics approvals. LT, MP and GF contributed to the study design, methodology and analysis plan. AH and JD provided clinical guidance, AH developed the outcome data sets and MP provided expertise in large administrative health databases housed at ICES in designing the study. HB drafted the initial manuscript and all authors critiqued the protocol manuscript.

FUNDING AND DATA SOURCES:

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CONFLICTS OF INTEREST:
The authors have no potential conflicts of interest to declare.

REFERENCES

1. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation. Chest 2018;154:1121–201. doi:10.1016/j.chest.2018.07.040
2. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease. Chest 2016;149:315–52. doi:10.1016/j.chest.2015.11.026
3. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330–93. doi:10.1093/eurheartj/ehy136
4. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv 2018;2:3257–91. doi:10.1182/bloodadvances.2018024893
5. Institute for Safe Medication Practices. ISMP list of high-alert medications in acute care settings. 2014.http://www.ismp.org/Tools/institutionalhighAlert.asp (accessed 25 May 2019).
6. Shehab N, Lovegrove MC, Geller AI, et al. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA 2016;316:2115. doi:10.1001/jama.2016.16201
7. Canadian Institute for Health Information. Adverse Drug Reaction–Related Hospitalizations Among Seniors, 2006 to 2011. Ottawa: 2013. https://secure.cihi.ca/free_products/Hospitalizations for ADR-ENweb.pdf
8. Holbrook A, Paterson M, Martins D, et al. Patient transitions and Oral Anticoagulant safety: A population-based cohort. Can J Cardiol 2018;34:S27–8. doi:10.1016/j.cjca.2018.07.367
9. Chen LM, Ayanian JZ. Care Continuity and Care Coordination. JAMA Intern Med 2014;174:749. doi:10.1001/jamainternmed.2013.14331
10. (CIHI) CI for HI. Physician Follow-Up After Hospital Discharge: Progress in Meeting Best Practices. Published Online First: 17 March 2015.https://secure.cihi.ca/estore/productFamily.htm?locale=en&pf=PFC2840 (accessed 17 May 2019).
11. World Health Organization. Continuity and coordination of care: A practical brief to support implemntation of the WHO Framework on integrated people-centred health services. Geneva: 2018.
12. Misky GJ, Wald HL, Coleman EA. Post-hospitalization transitions: Examining the effects of timing of primary care provider follow-up. J Hosp Med 2010;5:392–7. doi:10.1002/jhm.666
13. Lin CY, Barnato AE, Degenholtz HB. Physician Follow-Up Visits After Acute Care Hospitalization for Elderly Medicare Beneficiaries Discharged to Noninstitutional Settings. J Am Geriatr Soc 2011;59:1947–54. doi:10.1111/j.1532-5415.2011.03572.x
14. Shen E, Koyama SY, Huynh DN, et al. Association of a Dedicated Post–Hospital Discharge Follow-up Visit and 30-Day Readmission Risk in a Medicare Advantage Population. JAMA Intern Med 2017;177:132. doi:10.1001/jamainternmed.2016.7061
15. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship Between Early Physician Follow-up and 30-Day Readmission Among Medicare Beneficiaries Hospitalized for Heart Failure. JAMA 2010;303:1716. doi:10.1001/jama.2010.533
16. Sharma G, Kuo Y-F, Freeman JL, et al. Outpatient Follow-up Visit and 30-Day

Emergency Department Visit and Readmission in Patients Hospitalized for Chronic Obstructive Pulmonary Disease. Arch Intern Med 2010;170:1664–70. doi:10.1001/archinternmed.2010.345
17. Guay MOD, Tanzi S, Arregui MTSM, et al. Characteristics and outcomes of advanced cancer patients who miss outpatient supportive care consult appointments. Support Care Cancer 2014;22:2869–74. doi:10.1007/s00520-014-2254-8
18. Tung Y-C, Chang G-M, Chang H-Y, et al. Relationship between Early Physician Follow-Up and 30-Day Readmission after Acute Myocardial Infarction and Heart Failure. PLoS One 2017;12:e0170061. doi:10.1371/journal.pone.0170061
19. Howlett JG, McKelvie RS, Costigan J, et al. The 2010 Canadian Cardiovascular Society guidelines for the diagnosis and management of heart failure update: Heart failure in ethnic minority populations, heart failure and pregnancy, disease management, and quality improvement/assurance programs. Can J Cardiol 2010;26:185–202. doi:10.1016/S0828-282X(10)70367-6
20. Albert NM, Barnason S, Deswal A, et al. Transitions of Care in Heart Failure. Circ Hear Fail 2015;8:384–409. doi:10.1161/HHF.0000000000000006
21. Halasyamani L, Kripalani S, Coleman E, et al. Transition of care for hospitalized elderly patients—Development of a discharge checklist for hospitalists. J Hosp Med 2006;1:354–60. doi:10.1002/jhm.129
22. American College of Cardiology. Hospital to home. https://cvquality.acc.org/initiatives/hospital-to-home (accessed 25 May 2019).
23. Health Quality Ontario. Health Quality Ontario. Quality Monitor: 2010 Report on Ontario's Health System. Toronto: 2010. http://www.hqontario.ca/portals/0/Documents/pr/ qmonitor-full-report-2012-en.pdf
24. Health PEI. Chronic Obstructive Pulmonary Disease Clinical Pathway. Cbarlottetown: 2011. http://www.gov.pe.ca/photos/original/hpei_clinicalpa.pdf
25. Donaldson LJ, Kelley ET, Dhingra-Kumar N, et al. Medication Without Harm: WHO's Third Global Patient Safety Challenge. Lancet (London, England) 2017;389:1680–1. doi:10.1016/S0140-6736(17)31047-4
26. Aitken M, Gorokhovich L. Advancing the Responsible Use of Medicines: Applying Levers for Change. SSRN Electron J Published Online First: 17 September 2012. doi:10.2139/ssrn.2222541
27. Institute of Medicine. Preventing Medication Errors. Washington: The National Academic Press 2007.
28. Feigenbaum P, Neuwirth E, Trowbridge L, et al. Factors Contributing to All-cause 30-day Readmissions. Med Care 2012;50:599–605. doi:10.1097/MLR.0b013e318249ce72
29. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects—advantages and disadvantages. Nat Clin Pract Rheumatol 2007;3:725–32. doi:10.1038/ncprheum0652
30. Hashimoto RE, Brodt ED, Skelly AC, et al. Administrative database studies: goldmine or goose chase? Evid Based Spine Care J 2014;5:74–6. doi:10.1055/s-0034-1390027
31. Statistics Canada. Population estimates on July 1st, by age and sex. 2018. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501 (accessed 25 May 2019).
32. Schultz SE, Rothwell DM, Chen Z, et al. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. Chronic

Dis Inj Can 2013;33:160–6.http://www.ncbi.nlm.nih.gov/pubmed/23735455 (accessed 17 May 2019).

33. Jaakkimainen RL, Bronskill SE, Tierney MC, *et al.* Identification of Physician-Diagnosed Alzheimer's Disease and Related Dementias in Population-Based Administrative Data: A Validation Study Using Family Physicians' Electronic Medical Records. *J Alzheimer's Dis* 2016;54:337–49. doi:10.3233/JAD-160105
34. Hux JE, Ivis F, Flintoft V, *et al.* Diabetes in Ontario: Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25:512–6. doi:10.2337/diacare.25.3.512
35. Tu K, Chen Z, Lipscombe LL, et al. Prevalence and incidence of hypertension from 1995 to 2005: a population-based study. CMAJ 2008;178:1429–35. doi:10.1503/cmaj.071283
36. Tu K, Campbell NR, Chen Z-L, et al. Accuracy of administrative databases in identifying patients with hypertension. Open Med 2007;1:e18-26.http://www.ncbi.nlm.nih.gov/pubmed/20101286 (accessed 17 May 2019).
37. Tanuseputro P, Budhwani S, Bai YQ, et al. Palliative care delivery across health sectors: A population-level observational study. Palliat Med 2017;31:247–57. doi:10.1177/0269216316653524
38. Steinberg BA, Greiner MA, Hammill BG, et al. Contraindications to Anticoagulation Therapy and Eligibility for Novel Anticoagulants in Older Patients with Atrial Fibrillation. Cardiovasc Ther 2015;33:177–83. doi:10.1111/1755-5922.12129
39. Decousus H, Tapson VF, Bergmann J-F, et al. Factors at Admission Associated With Bleeding Risk in Medical Patients. Chest 2011;139:69–79. doi:10.1378/chest.09-3081
40. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv 2018;2:3198–225. doi:10.1182/bloodadvances.2018022954
41. MHASEF Research Team. Mental Health and Addictions System Performance in Ontario: A Baseline Scorecard. Toronto: 2018.
42. Wells G, Coyle D, Cameron C, et al. Safety, Effectiveness, and Cost-Effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation. Canadian Agency for Drugs and Technologies in Health 2012. http://www.ncbi.nlm.nih.gov/pubmed/24279001 (accessed 22 Jul 2019).
43. Linden CMJ van der, Jansen PAF, Geerenstein EV van, et al. Reasons for Discontinuation of Medication During Hospitalization and Documentation Thereof: A Descriptive Study of 400 Geriatric and Internal Medicine Patients. Arch Intern Med 2010;170:1081. doi:10.1001/archinternmed.2010.159
44. Viktil KK, Blix HS, Eek AK, et al. How are drug regimen changes during hospitalisation handled after discharge: a cohort study. BMJ Open 2012;2:e001461. doi:10.1136/BMJOPEN-2012-001461
45. Little D, Chai-Adisaksopha C, Hillis C, et al. Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis. Thromb Res 2019;175:102–9. doi:10.1016/j.thromres.2019.01.020
46. Levy AR, O'Brien BJ, Sellors C, et al. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2003;10:67–71.http://www.ncbi.nlm.nih.gov/pubmed/12879144 (accessed 16 May 2019).

47. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009;361:1139–51. doi:10.1056/NEJMoa0905561
48. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med 2011;365:883–91. doi:10.1056/NEJMoa1009638
49. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2011;365:981–92. doi:10.1056/NEJMoa1107039
50. Varadhan R, Weiss CO, Segal JB, et al. Evaluating Health Outcomes in the Presence of Competing Risks. Med Care 2010;48:S96–105. doi:10.1097/MLR.0b013e3181d99107
51. Andersen PK, Geskus RB, de Witte T, et al. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;41:861–70. doi:10.1093/ije/dyr213
52. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. Pharmacoepidemiol Drug Saf 2012;21:154–62. doi:10.1002/pds.2341
53. Sanfilippo KM, Wang T-F, Gage BF, et al. Improving accuracy of International Classification of Diseases codes for venous thromboembolism in administrative data. Thromb Res 2015;135:616–20. doi:10.1016/j.thromres.2015.01.012
54. Arnason T, Wells PS, van Walraven C, et al. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. Thromb Res 2006;118:253–62. doi:10.1016/j.thromres.2005.06.015
55. White RH, Garcia M, Sadeghi B, et al. Evaluation of the predictive value of ICD-9-CM coded administrative data for venous thromboembolism in the United States. Thromb Res 2010;126:61–7. doi:10.1016/j.thromres.2010.03.009
56. Birman-Deych E, Waterman AD, Yan Y, et al. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43:480–5.http://www.ncbi.nlm.nih.gov/pubmed/15838413 (accessed 24 Jun 2019)
57. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res 2008;43:1424–41.http://www.ncbi.nlm.nih.gov/pubmed/18756617 (accessed 16 May 2019).
58. Juurlink D, Preyra C, Croxford R, et al. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: 2006. https://www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information (accessed 28 May 2019).
59. Quan H, Li B, Couris CM, et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. Am J Epidemiol 2011;173:676–82. doi:10.1093/aje/kwq433
60. Pisters R, Lane DA, Nieuwlaat R, et al. A Novel User-Friendly Score (HAS-BLED) To Assess 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation. Chest 2010;138:1093–100. doi:10.1378/chest.10-0134
61. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124–d124. doi:10.1136/bmj.d124
62. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative Management of Antithrombotic Therapy. Chest 2012;141:e326S-e350S. doi:10.1378/chest.11-2298
63. Adam SS, McDuffie JR, Ortel TL, et al. Comparative Effectiveness of Warfarin and New Oral Anticoagulants for the Management of Atrial Fibrillation and Venous

Thromboembolism. Ann Intern Med 2012;157:796. doi:10.7326/0003-4819-157-10-201211200-00532
64. Hinojar R, Jiménez-Natcher JJ, Fernández-Golfín C, et al. New oral anticoagulants: a practical guide for physicians. Eur Hear J - Cardiovasc Pharmacother 2015;1:134–45. doi:10.1093/ehjcvp/pvv002
65. Vranckx P, Valgimigli M, Heidbuchel H. The Significance of Drug-Drug and Drug-Food Interactions of Oral Anticoagulation. Arrhythmia Electrophysiol Rev 2018;7:55–61. doi:10.15420/aer.2017.50.1
66. Sayani S, Iqbal O, Hoppensteadt D, et al. Drug Interactions of Newer Oral Anticoagulants Dabigatran, Rivaroxaban, and Apixaban with Routinely Used Nonanticoagulant/Antiplatelet Drugs. Blood 2014;124.
67. Liu A, Abrahamowicz M, Siemiatycki J. Conditions for confounding of interactions. Pharmacoepidemiol Drug Saf 2016;25:287–96. doi:10.1002/pds.3924
68. Health Quality Ontario. Quality in Primary Care: Setting a foundation for monitoring and reporting in Ontario. Toronto: 2015.
69. Lapointe-Shaw L, Mamdani M, Luo J, et al. Effectiveness of a financial incentive to physicians for timely follow-up after hospital discharge: a population-based time series analysis. CMAJ 2017;189:E1224–9. doi:10.1503/cmaj.170092
70. van Walraven C, Mamdani M, Fang J, et al. Continuity of care and patient outcomes after hospital discharge. J Gen Intern Med 2004;19:624–31. doi:10.1111/j.1525-1497.2004.30082.x
71. Williams JI and Young W, A Summary of Studies on the Quality of Health Care Administrative Databases in Canada. In Goel V, Williams JI, Anderson GM, Blackstien-Hirsch P, Fooks C, Naylor CD (eds). Patterns of Health Care in Ontario, The ICES Practice Atlas. 2nd edition. Ottawa: Canadian Medical Association, 1996:339-345.
72. Kyriacou DN, Lewis RJ. Confounding by Indication in Clinical Research. JAMA 2016;316:1818. doi:10.1001/jama.2016.16435
73. Csizmadi I, Collet J-P, Boivin J-F. Bias and Confounding in Pharmacoepidemiology. In: Pharmacoepidemiology. Chichester, UK: : John Wiley & Sons, Ltd 791–809. doi:10.1002/9780470059876.ch47
74. Austin PC, Mamdani MM, van Walraven C, et al. Quantifying the impact of survivor treatment bias in observational studies. J Eval Clin Pract 2006;12:601–12. doi:10.1111/j.1365-2753.2005.00624.x
75. Ogundimu EO, Altman DG, Collins GS. Adequate sample size for developing prediction models is not simply related to events per variable. J Clin Epidemiol 2016;76:175–82. doi:10.1016/j.jclinepi.2016.02.031
76. Faraway JJ. Does data splitting improve prediction? Stat Comput 2016;26:49–60. doi:10.1007/s11222-014-9522-9
77. Picard RR, Berk KN. Data Splitting. Am Stat 1990;44:140. doi:10.2307/2684155
78. Royston P, Moons KGM, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. BMJ 2009;338:b604. doi:10.1136/bmj.b604
79. Derksen S, Keselman HJ. Backward, forward and stepwise automated subset selection algorithms: Frequency of obtaining authentic and noise variables. Br J Math Stat Psychol 1992;45:265–82. doi:10.1111/j.2044-8317.1992.tb00992.x
80. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat

Med 1996;15:361–87. doi:10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4
81. Uchino K, Hernandez A V. Dabigatran Association With Higher Risk of Acute Coronary Events. Arch Intern Med 2012;172:397. doi:10.1001/archinternmed.2011.1666
82. Clemens A, Fraessdorf M, Friedman J. Cardiovascular outcomes during treatment with dabigatran: comprehensive analysis of individual subject data by treatment. Vasc Health Risk Manag 2013;9:599–615. doi:10.2147/VHRM.S49830
83. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation 2016;133:601–9. doi:10.1161/CIRCULATIONAHA.115.017719

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-13
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-17
		(*b*) Describe any methods used to examine subgroups and interactions	16
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	16
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A

Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Predictors of Oral Anticoagulant-associated Adverse Events in Seniors Transitioning from Hospital to Home: A Retrospective Cohort Study Protocol

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TITLE: Predictors of Oral Anticoagulant-associated Adverse Events in Seniors Transitioning from Hospital to Home: A Retrospective Cohort Study Protocol

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ABSTRACT:

Introduction

Oral anticoagulants (OACs) are widely prescribed in older adults. High OAC-related adverse event rates in the early period following hospital discharge argue for an analysis to identify predictors. Our objective is to identify and validate clinical and continuity of care variables amongst seniors discharged from hospital on an OAC, which are independently associated with OAC-related adverse events within 30 days.

Methods and Analysis

We propose a population-based retrospective cohort study of all adults aged 66 years or older who were discharged from hospital on an oral anticoagulant from September 2010 to March 2015 in Ontario, Canada. The primary outcome is a composite of the first hospitalization or Emergency Department visit for a hemorrhage or thromboembolic event or mortality within 30 days of hospital discharge. A Cox proportional hazards model will be used to determine the association between the composite outcome and a set of prespecified covariates. A split sample method will be adopted to validate the variables associated with OAC-related adverse events.

Ethics and Dissemination

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. Results will be disseminated via peer-reviewed publications and presentations at conferences and will determine intervention targets to improve OAC management in upcoming randomized trials.

Strengths and Limitations

- Few studies have examined factors that predict medication safety adverse events during periods of transitions of care.
- In this large, population-based cohort study of seniors, we examine both clinical and continuity of care risk factors for oral anticoagulant (OAC)- related adverse events post-hospitalization.
- This study is subject to the limitations inherent in observational design and the use of health administrative databases.

INTRODUCTION

Background/Rationale

Oral anticoagulants (OACs) are commonly prescribed for the prevention and treatment of stroke, systemic embolism and venous events associated with atrial fibrillation (AF) and venous thromboembolism (VTE) [1-3]. Despite the introduction of direct-acting oral anticoagulants (DOACs), which do not require routine laboratory monitoring and are associated with less bleeding than warfarin, OACs remain a top cause of serious drug-related harm, primarily bleeding and thromboembolic events [4,5].

It is estimated that between 2013 and 2014 OACs were implicated in 28% (95% confidence interval [CI)] 23-32%) and 39% (95% CI 33.7-43.8%) of emergency department (ED) visits in the United States for adverse drug events among adults aged 65 to 79 years and those 80 years or older, respectively [6]. In Canada, it is estimated that OACs account for 12.6% of adverse drug reaction-related hospitalizations among seniors between 2006 and 2011 [7].

Observational studies using population-level data report even higher adverse event rates for OAC users during periods of transitions in care, specifically during the early post-hospitalization period. Amongst the elderly, a bleeding risk of 26.4% (95% confidence interval [CI] 25.3-27.4) per person-year, and a thromboembolic event risk of 32.4% (95% CI 31.3-33.5) per person-year, were identified in OAC users within the first 30-days after hospital discharge [8].

The high rates of adverse events in the early post-discharge period suggest that continuity of care during this hectic time for patients transitioning out of the hospital may be part of the problem [9,10]. Continuity of care is defined by the World Health Organization as "the degree to which discrete health care events are experienced by people as coherent and interconnected over time and consistent with their health needs and preferences" [11]. Several studies have found that prompt primary care follow-up of patients after hospital discharge reduces subsequent ED visits and hospitalizations among patients with chronic conditions such as congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction and cancer [12-18]. Many clinical practice guidelines recommend physician follow-up within 1-2-weeks post-discharge as best practice to improve continuity of care [10,19-24].

Coordinating medication management post-hospitalization is challenging, with adverse drug events reported as among the most common reason for post-discharge readmission and ED visits [25-27]. Poor medication management immediately following hospital discharge has been reported to increase the risk of 30-day readmission by 28% [28]. Therefore, understanding which factors, including patient, hospital, provider, and medication-related factors, predict adverse clinical outcomes, will be important to reducing adverse outcomes, re-admissions and costs.

This study aims to identify important risk factors, both clinical and continuity of care, which predict OAC-related harm in the short-term period following hospitalization. Validated process of care risk factors may be useful targets for future intervention trials.

Objectives

Research Question: Among Ontario residents aged 66 years or older who were discharged from hospital on an OAC (warfarin, dabigatran, rivaroxaban, or apixaban), which clinical and continuity of care variables are significantly associated with time to re-hospitalization or an emergency department visit for a hemorrhage or thromboembolic event, or mortality within 30 days post-discharge?

Hypothesis: In addition to traditional clinical risk factors for OAC-related adverse events, factors related to continuity of care, particularly contact with a primary care physician, nurse practitioner, medical specialist or home care services within 7 days of discharge, will be associated with lower risk for the composite outcome in the 30 days following hospitalization.

METHODS AND ANALYSIS

Reporting will be compliant with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Study Design

We will use a population-based retrospective cohort study to identify potential patient, provider, and institution-level factors and continuity of care factors independently associated with OAC-related adverse events in seniors using routinely collected administrative health data. These data are more accurate than self-reported data and minimize selection bias as the database includes the entire population of interest [29,30].

Setting

Our study will be set in Ontario, Canada. Ontario is Canada's most populous province, with over 14 million residents in 2018, representing about 39% of the country's population [31].

Data Sources

The study dataset will be created using the province of Ontario's health administrative databases housed at ICES. These databases contain administrative health service records for the approximately 14 million Ontarians eligible for health coverage [32-36]. These databases are linked using encrypted patient-specific identifiers. Table 1 summarizes the database names and contents of those that will be used to create the study dataset.

Table 1: Description of ICES Databases

Name of Database	Content of Database
Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	Patient-level demographic, diagnostic, procedural and treatment information on all acute care hospitalizations
CIHI—National Ambulatory Care Reporting System (CIHI-NACRS)	Patient-level demographic, diagnostic, procedural and treatment information for all hospital-based and community-based ambulatory care
Client Agency Program Enrollment Database (CAPE)	Information regarding enrollment of individuals with primary care practitioners, teams and networks
ICES-Derived Cohorts	Validated cohorts of individuals with specific diseases and conditions. These include: the Ontario Congestive Heart Failure (CHF) Database [37]; Ontario Dementia Database (DEMENTIA) [38]; Ontario Diabetes

	Database (ODD) [39]; Ontario Hypertension Dataset (HYPER) [40,41]
ICES Physician Database (IPDB)	Characteristics of physicians and surgeons licenced to practice in Ontario
Ontario Cancer Registry (OCR)	Patient-level demographic, cancer diagnosis and cancer-related mortality information
Ontario Continuing Care Reporting System (CCRS)	Demographic, clinical, functional and resource utilization information on individuals receiving hospital-based complex continuing care services
Ontario Drug Benefit Program Database (ODB)	Records of dispensed outpatient prescriptions paid for by the provincial government
Ontario Health Insurance Plan Claims History Database (OHIP)	Claims for physician services paid for by the provincial government
Ontario Health Insurance Plan Registered Persons Database (RPDB)	Demographic, place of residence and vital status information for all persons eligible to receive insured heath services in the province
Ontario Home Care Database (HCD)	Patient-level demographic, diagnostic, procedural and treatment information on all home care visits
Ontario Mental Health Reporting System Database (OMHRS)	Patient-level demographic, diagnostic, procedural and treatment information on all adult inpatient mental health visits
Ontario Ministry of Health and Long-Term Care Institution Information System	Ontario health care institution information
Resident Assessment Instrument—Contact Assessment (RAI-CA)	Patient-level demographics, diagnosis and treatment information used to guide intake of patients into home care services
Resident Assessment Instrument—Home Care (RAI-HC)	Contains data that assesses the care and needs of adult patients in hospital and community settings for in-home and placement services
Statistics Canada Census Postal Code Conversion File	Information on rural residence and income quintiles of residents

Observation Period

We define the study's index date as the date of OAC dispensing, which had to be within one day of hospital discharge. The patient accrual period will be September 1, 2010 through March 31, 2015. This period captures the time following the approval of DOACs by Health Canada and allows for a sufficient sample size to conduct this study [42].

We will define a 7-day post-discharge blanking period during which patients will have been dispensed an index OAC, but study outcome events will not be measured. All patients who died or experienced a hospitalization or an ED visit for a thromboembolic or hemorrhagic event within the 7-day blanking period will be excluded. For those who remain in the cohort, health care contacts during the blanking period will be recorded.

Patients will be followed from the end of the blanking period (Day 8) until day 30 post-hospitalization (or a maximum follow-up of 24 days), with the last outcome event date being 30

April 2015. We will assume that all patients continuously use OACs during follow-up. However, patients will be censored at a hospitalization lasting more than 5 days, as information on in-hospital medications are not available in administrative claims data and medications are often changed or discontinued during hospital admission [43,44].

Participants

Inclusion and Exclusion Criteria

The source population will be all Ontario residents aged 66 years or older who are discharged from an acute care hospital and dispensed a single OAC - warfarin, dabigatran, apixaban or rivaroxaban at any dose, within one day of discharge. Patients with a most responsible discharge diagnosis of major bleeding, defined as any bleeding event that was the cause for the hospitalization or contributed to the greatest fraction of the length of stay, will be excluded [45]. We will use the Ontario Health Insurance Plan (OHIP) Registered Persons Database (RPDB), which contains insurance coverage, demographic, place of residence and vital status information, together with the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), to identify the study patients. We will also access the prescription drug claims history of eligible patients via the Ontario Drug Benefit Plan Database (ODB). These datasets are linked using unique coded identifiers and will be analyzed at ICES (www.ices.on.ca).

The age threshold of 66 years will be applied to capture prescription use by study participants at least 1-year prior to study enrollment, as Ontario Drug Benefits program eligibility begins at the age of 65. This will avoid incomplete or missing prescription drug data for study participants [46].

Variables

Outcomes

The primary outcome will be a composite of hospitalization or ED visit for a hemorrhage or thromboembolic event, or death from any cause. These events are standard in pivotal trials and are the main OAC-associated serious adverse events. Including death also avoids the problem of competing risks [47-51].

Thromboembolic events will include venous thromboembolic events (deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (ischemic stroke or transient ischemic attack, peripheral vascular disease or emergency rescue procedure, or systemic embolism). The International Classification of Diseases (ICD) 10th revision diagnosis codes, and the Canadian Classification of Health Interventions procedure codes for these conditions are provided in Table 2. Validation studies have found equivalent ICD 9 diagnosis codes to have 91% sensitivity and 95% specificity [52-56]. Hemorrhagic events will include intracranial bleeds, upper and lower gastrointestinal bleeds, and any other bleed which required a hospital admission or a visit to an ED. Table 3 lists the ICD 10 diagnosis codes used to define hemorrhage. Validation studies found equivalent ICD 9 diagnosis codes to have 94% sensitivity and 83% specificity for major hemorrhagic events [54].

Table 2: Diagnosis and Procedure codes used to define thromboembolic outcomes

Thromboembolic Event Type	ICD10 Codes	Canadian Classification of Healthcare Interventions Codes

Deep Vein Thrombosis	I82.8, I82.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.0, I82.1, I82.2, I82.3	
Pulmonary Embolism	I26.0, I26.9	
Ischemic Stroke	I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, 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	I70.0, I70.1, I70.20, I70.21, I70.8, I70.9, I73.1, I73.8, I73.9, K55.1	1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76, 1KG87, 1IA87, 1IB87, 1IC87, 1ID87, 1KA87, 1KE57
Systemic Embolism	I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9	

Table 3: Diagnosis codes used to define hemorrhage outcomes

Hemorrhage Type	**ICD10 Codes**
Intracerebral	I60, I61, I62.0, I62.1, I62.9, S06.400, S06.401, S06.410, S06.411, S06.420, S06.421, S06.430, S06.431, S06.440, S06.441, S06.490, S06.491, S06.500, S06.501, S06.510, S06.511, S06.520, S06.521, S06.530, S06.531, S06.540, S06.541, S06.590, S06.591, S06.600, S06.601, S06.610, S06.611, S06.620, S06.621, S06.630, S06.631, S06.640, S06.641, S06.690, S06.691
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, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K63.80, K31.80, K92.0, K92.1, K92.2
Lower Gastrointestinal	K55.20, K62.5
Other	N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, K66.1, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R31.0, R31.1, R31.8, R58, D68.3, H35.6, H43.1, H45.0, M25.0

The outcomes will be ascertained using CIHI-DAD, CIHI-NACRS and RPDB [57,58].

Risk Factors

Table 4 summarizes the clinical and continuity of care risk factors being explored in this project, as well as their data sources. Patient demographic characteristics captured as of the date of cohort entry will include age, sex, socioeconomic status (as defined by census neighborhood income quintiles), rural residence, and whether the patient is rostered with a primary care

physician. In addition, palliative patients will also be identified using a previously validated combination of codes in health administrative databases [37].

Table 4: Clinical and Continuity of Care variables and data sources

Variable	Data Source
Patient Characteristics	
Age	RPDB
Sex	
Income Quintile	Statistics Canada Census Postal Code Conversion File
Rural Residence	
Rostering – patient enrolled in a primary care organization, team or with a primary care physician	CAPE
Palliative Patient – lookback window of 6 months	OHIP, CIHI-DAD, CIHI-NACRS, RAI-CA, RAI-HC, HCD, CCRS
Characteristics of Index Hospitalization	
Type of hospital- Teaching, Community, Small	Ontario Ministry of Health and Long-Term Care
Length of index hospitalization	CIHI-DAD
Specialty of the physician responsible for index OAC prescription- General/Family Practitioner; Cardiology; Hematology; Internal Medicine; Orthopedic Surgery; Oncology; Other Surgery; Other	IPDB
Type of OAC dispensed at index prescription date- Warfarin, Apixaban, Dabigatran, Rivaroxaban	ODB
Type of discharge – Home; Long term or Continuing care facility; Other	CIHI-DAD
Type of OAC User	
Incident-patients who were not dispensed an OAC in the year prior to cohort entry	ODB
Prevalent	
Non-switchers- patients who were dispensed the same OAC in the year prior to cohort entry	
Switchers- patients who were dispensed a different OAC in the year prior to cohort entry	
Comorbidities	
Components of CHA2DS2-VASc* (Not including those mentioned above) – looking at the presence of these medical conditions in the 3 years prior to cohort entry	
Congestive Heart Failure	CHF
Hypertension	HYPER
Diabetes Mellitus	ODD
Prior stroke/ Transient Ischemic Stroke	CIHI-DAD
Peripheral Vascular Disease	
Components of HAS-BLED** (Not including those mentioned above) – looking at the presence of these medical conditions in the 3 years prior to cohort entry	

Abnormal renal/liver function	CIHI-DAD, OHIP
Prior bleeding	CIHI-DAD
Drugs/alcohol concomitantly	CIHI-DAD, ODB
Charlson Comorbidity Score	CIHI-DAD
Other comorbidities	
Dementia	DEMENTIA
Delirium	CIHI-DAD, OMHRS
Diagnosis of obesity in the 3 years prior to cohort entry	CIHI-DAD, OHIP
Diagnosis of underweight in the 3 years prior to cohort entry	
Antiphospholipid syndrome in the 3 years prior to cohort entry	CIHI-DAD
Active cancer	OCR, OHIP
Thromboembolic event	CIHI-DAD, CIHI-NACRS
Substance Abuse	CIHI-DAD, OMHRS, OHIP
Alcoholic Abuse	
Number of hospitalizations in the past year	CIHI-DAD
Recent Anticoagulant use (120 d)	ODB
Indications	
Atrial fibrillation	CIHI-DAD, CIHI-NACRS, OHIP
Joint replacement	CIHI-DAD
Major surgery	CIHI-DAD
Deep vein thrombosis or Pulmonary Embolism	CIHI-DAD, CIHI-NACRS
Mechanical heart valve	CIHI-DAD
Potential Drug Interactions- dispensed in the past 120 days prior to cohort entry, unless otherwise specified	
Non-Steroidal Anti-Inflammatory Drugs***	ODB
Selective Serotonin Reuptake Inhibitors	
Amiodarone	
Aspirin***	
Antiplatelets	
Antibiotics, dispensed in the past 30 days prior to cohort entry	
Number of drugs dispensed which potentially interact with OACs	
Continuity of Care- Health care contact within 7 days of discharge from index hospitalization	
Follow up with primary care physician, nurse practitioner, medical specialist or home care services	OHIP, HCD
Follow up with familiar hospital physician	OHIP
Follow up with familiar community physician	OHIP

Data Sources: RPDB- Ontario Health Insurance Plan Registered Persons Database; CAPE- Client Agency Program Enrollment Database; OHIP- Ontario Health Insurance Plan Claims History Database; CIHI-DAD - Canadian Institute for Health Information–Discharge Abstract Database; CIHI-NACRS - CIHI—National Ambulatory Care Reporting System; RAI-CA - Resident Assessment Instrument—Contact Assessment; RAI-HC - Resident Assessment Instrument—Home Care; HCD- Ontario Home Care Database; CCRS- Ontario Continuing Care Reporting System; IPDB- ICES Physician Database; ODB- Ontario Drug Benefit Program Database; CHF- Congestive Heart Failure

database; HYPER- Ontario Hypertension Dataset (HYPER); ODD- Ontario Diabetes Database; DEMENTIA- Ontario Dementia Database; OMHRS- Ontario Mental Health Reporting System Database; OCR- Ontario Cancer Registry; HCD- Ontario Home Care Database.
**CHA2DS2-VASc- Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category.*
***HAS-BLED- Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (excluded), Elderly (>65 years), Drugs/alcohol concomitantly.*
**** Over-the-counter use of drug is not captured.*

Characteristics of the index hospitalization including type of hospital, length of index hospitalization and type of discharge will be captured. We will also capture specialty of the physician responsible for index OAC prescription and OAC dispensed at index prescription date. The cohort will be categorized into three categories of OAC users including incident, prevalent non-switchers and prevalent switchers.

Existing comorbidities may be associated with outcomes [38-40]; therefore, comorbidities including dementia and diabetes will be captured [33,34]. In addition, patients with a history of substance or alcohol abuse in the past 3 years prior to cohort entry will be identified [41]. A diagnosis of obesity, underweight, antiphospholipid syndrome, and delirium will also be captured. Patients with active cancer, defined as individuals who received a cancer diagnosis, cancer related surgery, chemotherapy or radiation in the past 180 days, will be identified. Hospitalization or ED visits in the 3 years prior to cohort entry for thromboembolic or hemorrhagic events will also be recorded.

Several indices, including the Deyo-Charlson Comorbidity Index, a general comorbidity measure developed to predict mortality, also will be calculated to describe the cohort [59]. Validated clinical scores used to guide anticoagulation of patients including the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category) risk stratification scheme for predicting thromboembolism in patients with atrial fibrillation will be calculated [60]. Additionally, the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly) score which was developed to support clinical decision-making regarding anticoagulant therapy in AF patients by predicting bleeding risk in these patients will be calculated [61]. Since data on labile international normalized ratio is not available this will not be calculated as part of the score.

Indications that result in the prescription of OACs will also be recorded to control for confounding by indication including presence of AF in the 10 years prior to cohort entry, joint replacement (hip or knee arthroplasty) in the 35 days prior to cohort entry, major surgery lasting 120 minutes or longer (excluding same day surgery) during index hospitalization, presence of a mechanical heart valve, and deep vein thrombosis or pulmonary embolism during index hospitalization [62-64]. These indications will be inferred from corresponding diagnosis and procedure information, as indications for prescriptions are not recorded in Ontario prescription drug claims.

We will be adjusting for the presence of drug therapies hypothesized to influence the risk of our outcome through potential interactions with OACs by including use of prescription nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), amiodarone, prescription aspirin, and antiplatelets use in the 120 days prior to cohort entry and antibiotic use in the 30 days prior to cohort entry [64-66]. Recent pre-hospital anticoagulant use was also captured.

Continuity of care will be operationalized to measure whether follow-up was performed by a primary care physician, nurse practitioner, medical specialist, or home care services within 7 days of discharge. This measure will help gauge how well outpatient care is coordinated with hospital care as this is an important aspect of care coordination which may help reduce hospital readmissions [67,68]. In addition, we will capture whether patients had a follow up visit within 1-week post-discharge with any physician with whom they had had at least 2 visits in the 12 months preceding the index hospitalization (community physician) or at least 1 visit during the hospital stay (hospital physician) [10]. Research studies have reported that seeing a physician who is familiar with the patient's health post-hospitalization may have a beneficial impact on follow-up rates and reduce risk of death or readmissions [69].

Quality checks, missing data and extreme values

Data are unlikely to be missing at random [46,58,70]. For categorical variables an additional 'missing' category will be included. If ≥ 10% of observations are missing multiple imputations are planned.

Bias

Bias in pharmacoepidemiology studies results from multiple sources of confounding [67,71,72]. DOAC users tend to be younger with fewer comorbidities than warfarin users [73]. To control for confounding, we will include variables such as age, sex, presence of specific comorbidities, concomitant medications, remote residence, neighbourhood income quintile, and physician specialty amongst other independent variables in the model as potential risk factors. Furthermore, the inclusion criteria for study participants may exclude prevalent OAC users who have an existing supply of OACs. This biases the study cohort to include more patients who start OAC therapy post-hospitalization. However, the current participant inclusion criteria allow us to study the impact of the index hospitalization on outcomes for OAC users.

Given that continuity of care risk factors are hypothesized to be important in the early period after hospital discharge for OAC-related adverse events, the outcome observation period will begin after 7-days post-discharge to avoid survivor-treatment bias [74]. We will report the number of patients excluded due to the occurrence of an event during the blanking period.

Sample Size

For Cox regression, a fitted model is likely to be reliable and stable when the number of participants with the outcome (ie, either first hospitalization or ED visit during follow-up for a hemorrhage or arterial or venous thromboembolic event, or death) is 20 times the number of covariates [75]. We anticipate that up to 30 covariates will be included in the Cox regression model; therefore, a minimum of 600 patients with at least one of the outcomes that form the composite will be required to devise the models in this cohort. This is feasible as a similar study reported haemorrhage and thromboembolic event rates of about 26 and 34 per 100 person-years in the first 30 days post-discharge, respectively in a cohort of 123,140 patients [8]. In addition, the long accrual period will also help ensure a sufficient sample size.

Statistical Plan

All data will be examined using descriptive statistics. Categorical variables will be summarized using frequency and percentage. Continuous variables will be summarized using

mean and standard deviation (SD) or median and interquartile range (IQR), when results are skewed. Person-time of follow-up will also be captured.

A summary of all planned analysis is provided in Table 5. Given that the primary outcome is a time-to-event outcome, Cox proportional hazards model will be used to determine the association between the composite outcome and all risk factors including patient demographic, index hospitalization descriptors, comorbidity, drug indications, potential drug interactions and continuity of care variables within one-month of hospital discharge.

Table 5: Statistical Plan Summary

Objective/Analyses	**Outcome**		**Method of Analysis**	**Independent Variables**
Primary Objective	Definition	Type		
To determine which clinical and continuity of care variables predict the outcome in senior OAC users post-hospitalization	Re-hospitalization or ED visit for a hemorrhagic or thromboembolic event or mortality in 30-days	Time to event	Cox Proportional Hazards Model	*Demographic* • Income quintile • Rural residence • Patients enrolled under a primary care physician or organization • Palliative Patient *Index Hospitalization Characteristics* • Type of hospital • Specialty of OAC prescribing physician • Type of OAC dispensed • Type of discharge *Type of OAC user* • Incident • Prevalent Non-switcher • Prevalent Switcher *Comorbidities* • CHA2DS2-VASc* • HASBLED** • Dementia • Delirium • Obesity • Underweight • Antiphospholipid syndrome • Active cancer • Prior thromboembolic or hemorrhagic event • Substance abuse • Alcohol abuse • Hospitalization in past year
Sensitivity Analyses				
Include myocardial infarction in the definition of thromboembolic event outcome	Re-hospitalization or ED visit for a hemorrhagic or thromboembolic event or mortality in 30-days	Time to event	Cox Proportional Hazards Model	
Competing Risk Analysis	Re-hospitalization or ED visit for a hemorrhagic or thromboembolic event in 30-days	Time to event	Cause-specific Cox proportional hazards model	
Validation				
Internal validation of the primary model	Re-hospitalization or ED visit for a hemorrhagic or thromboembolic event or mortality in 30-days	Time to event	Split-Sample Method	

				• Recent anticoagulant use Indications • Atrial Fibrillation • Joint replacement • Major surgery • Mechanical heart valve • Deep vein thrombosis or Pulmonary embolism *Potential Drug Interactions* • NSAIDs*** • SSRIs • Amiodarone • Aspirin*** • Antiplatelets • Antibiotics • Number of drugs, potentially drugs interacting with OACs, dispensed *Continuity of Care* • Follow up with primary care physician, nurse practitioner, medical specialist or home care services within 7 days of discharge from index hospitalization

**CHA2DS2-VASc- Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category.*

***HAS-BLED- Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (excluded), Elderly (>65 years), Drugs/alcohol concomitantly.*

**** Over-the-counter use of drug is not captured.*

Model Construction

Model derivation and validation will be based on a split-sample method [76]. Two-thirds of the study participants will be randomly assigned to a model derivation cohort, and one-third will be reserved as an independent validation cohort [77]. Both cohorts will be compared with respect to clinical and continuity of care variables.

The model will be developed based on data from the derivation cohort alone. For the primary outcome, because predictors that are highly correlated with others contribute little independent information, pruning candidate predictors will be required [78]. The effect of multicollinearity between predictors would inflate the variance of the coefficient estimates and makes the estimates very sensitive to minor changes in the model. To avoid this, multicollinearity amongst the covariates will be explored using tolerance statistics and variance inflation factor. Tolerance statistic of below 0.1 and a variance inflation factor of above 10 will indicate multicollinearity. Of the highly correlated independent variables one will be removed from the model based on clinical judgement.

Subsequently, univariate Cox regression models will be used to select variables for entry into the multivariable regression model. If the p-value of a variable is less than or equal to 0.20 that variable will be included in the model building stage of the final multivariate regression model.

To investigate whether significant covariates can modify the effect of other predictors in the Cox proportional hazards model, two-way interactions between clinically significant predictors will be tested. Significant interactions with a p-value of ≤0.05 will be retained and added into the prediction model.

Finally, since this is an exploratory analysis, a backward stepwise approach will be employed for selection of risk factors for inclusion in the final multivariate Cox model [79]. Least significant independent variables including confounding variables will be removed until all p-values are below 0.2. The continuity of care variable, hypothesized to significantly impact the survival of the patient, will be retained in the model. Risk factors with the effects from the Cox proportional hazard's model expressed as the HR, corresponding 95% CI and the associated *p*-value will be reported. The proportionality assumption will be assessed using Schonfeld residuals and interaction of risk factors with time [80]. If proportionality assumption is not met results will be stratified if appropriate. All violations of the proportionality assumption will be reported.

Sensitivity Analysis

There is much debate on effect of oral anticoagulants on acute myocardial infarction. Meta-analyses of RCTs have concluded that the use of dabigatran is associated with an increased risk of acute myocardial infarction [81,82]. Given the evidence on risk for acute myocardial infarction in dabigatran users, a sensitivity analysis with this event in the definition of the composite outcome will be performed using the aforementioned methods.

Moreover, a competing risk analysis is planned where all-cause mortality will be treated as a competing risk for hemorrhagic and thromboembolic events. A cause-specific Cox proportional hazards model will be constructed [83]. Predictors and their coefficients in the cause-specific hazard models will be compared with those in the full Cox model.

Model Validation

Once the final model is developed, it will be assessed in the separate validation cohort of patients. The predictive accuracy of the model will be assessed using tests for discrimination and calibration [80]. We will evaluate the model calibration by conducting the Gronnesby and Borgan

Test which uses martingale residuals to compare the count of events to the semi-parametric estimates from the Cox proportional hazards model on a cumulative hazards scale [80]. Discrimination will be evaluated using Harell's C-index representing the area under the receiver operating characteristic curve with larger values indicating better discrimination [80].

Data management and analysis will be performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient and Public Involvement

The publicly funded research program that includes this study has several patient co-investigators and advisors. Input from 19 patients participating in focus groups on barriers and facilitators for optimal oral anticoagulant management, provided suggestions for predictors. Patients did not contribute to the actual writing or editing of this document.

ETHICS AND DISSEMINATION

All study data reside and are analyzed at ICES (www.ices.on.ca). ICES is a prescribed entity under Section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45, and was approved by ICES' Privacy and Legal Office.

The results of this study will be published in a peer-reviewed journal and presented at national and international conferences. They will also help determine intervention targets to improve OAC management in upcoming randomized trials.

AUTHOR CONTRIBUTIONS:

AH obtained the funding and developed the study idea. HB and AH designed the study. HB obtained data permissions and research ethics approvals. LT, MP and GF contributed to the study design, methodology and analysis plan. AH and JD provided clinical guidance, AH developed the outcome data sets and MP provided expertise in large administrative health databases housed at ICES in designing the study. HB drafted the initial manuscript and all authors critiqued the protocol manuscript.

FUNDING AND DATA SOURCES:

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CONFLICTS OF INTEREST:

The authors have no potential conflicts of interest to declare.

REFERENCES

1. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation. Chest 2018;154:1121–201. doi:10.1016/j.chest.2018.07.040
2. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease. Chest 2016;149:315–52. doi:10.1016/j.chest.2015.11.026
3. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330–93. doi:10.1093/eurheartj/ehy136
4. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv 2018;2:3257–91. doi:10.1182/bloodadvances.2018024893
5. Institute for Safe Medication Practices. ISMP list of high-alert medications in acute care settings. 2014.http://www.ismp.org/Tools/institutionalhighAlert.asp (accessed 25 May 2019).
6. Shehab N, Lovegrove MC, Geller AI, et al. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA 2016;316:2115. doi:10.1001/jama.2016.16201
7. Canadian Institute for Health Information. Adverse Drug Reaction–Related Hospitalizations Among Seniors, 2006 to 2011. Ottawa: 2013. https://secure.cihi.ca/free_products/Hospitalizations for ADR-ENweb.pdf
8. Holbrook A, Paterson M, Martins D, et al. Patient transitions and Oral Anticoagulant safety: A population-based cohort. Can J Cardiol 2018;34:S27–8. doi:10.1016/j.cjca.2018.07.367
9. Chen LM, Ayanian JZ. Care Continuity and Care Coordination. JAMA Intern Med 2014;174:749. doi:10.1001/jamainternmed.2013.14331
10. (CIHI) CI for HI. Physician Follow-Up After Hospital Discharge: Progress in Meeting Best Practices. Published Online First: 17 March 2015.https://secure.cihi.ca/estore/productFamily.htm?locale=en&pf=PFC2840 (accessed 17 May 2019).
11. World Health Organization. Continuity and coordination of care: A practical brief to support implemntation of the WHO Framework on integrated people-centred health services. Geneva: 2018.
12. Misky GJ, Wald HL, Coleman EA. Post-hospitalization transitions: Examining the effects of timing of primary care provider follow-up. J Hosp Med 2010;5:392–7. doi:10.1002/jhm.666
13. Lin CY, Barnato AE, Degenholtz HB. Physician Follow-Up Visits After Acute Care Hospitalization for Elderly Medicare Beneficiaries Discharged to Noninstitutional Settings. J Am Geriatr Soc 2011;59:1947–54. doi:10.1111/j.1532-5415.2011.03572.x
14. Shen E, Koyama SY, Huynh DN, et al. Association of a Dedicated Post–Hospital Discharge Follow-up Visit and 30-Day Readmission Risk in a Medicare Advantage Population. JAMA Intern Med 2017;177:132. doi:10.1001/jamainternmed.2016.7061
15. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship Between Early Physician Follow-up and 30-Day Readmission Among Medicare Beneficiaries Hospitalized for Heart Failure. JAMA 2010;303:1716. doi:10.1001/jama.2010.533
16. Sharma G, Kuo Y-F, Freeman JL, et al. Outpatient Follow-up Visit and 30-Day

Emergency Department Visit and Readmission in Patients Hospitalized for Chronic Obstructive Pulmonary Disease. Arch Intern Med 2010;170:1664–70. doi:10.1001/archinternmed.2010.345

17. Guay MOD, Tanzi S, Arregui MTSM, et al. Characteristics and outcomes of advanced cancer patients who miss outpatient supportive care consult appointments. Support Care Cancer 2014;22:2869–74. doi:10.1007/s00520-014-2254-8
18. Tung Y-C, Chang G-M, Chang H-Y, et al. Relationship between Early Physician Follow-Up and 30-Day Readmission after Acute Myocardial Infarction and Heart Failure. PLoS One 2017;12:e0170061. doi:10.1371/journal.pone.0170061
19. Howlett JG, McKelvie RS, Costigan J, et al. The 2010 Canadian Cardiovascular Society guidelines for the diagnosis and management of heart failure update: Heart failure in ethnic minority populations, heart failure and pregnancy, disease management, and quality improvement/assurance programs. Can J Cardiol 2010;26:185–202. doi:10.1016/S0828-282X(10)70367-6
20. Albert NM, Barnason S, Deswal A, et al. Transitions of Care in Heart Failure. Circ Hear Fail 2015;8:384–409. doi:10.1161/HHF.0000000000000006
21. Halasyamani L, Kripalani S, Coleman E, et al. Transition of care for hospitalized elderly patients—Development of a discharge checklist for hospitalists. J Hosp Med 2006;1:354–60. doi:10.1002/jhm.129
22. American College of Cardiology. Hospital to home. https://cvquality.acc.org/initiatives/hospital-to-home (accessed 25 May 2019).
23. Health Quality Ontario. Health Quality Ontario. Quality Monitor: 2010 Report on Ontario's Health System. Toronto: 2010. http://www.hqontario.ca/portals/0/Documents/pr/ qmonitor-full-report-2012-en.pdf
24. Health PEI. Chronic Obstructive Pulmonary Disease Clinical Pathway. Cbarlottetown: 2011. http://www.gov.pe.ca/photos/original/hpei_clinicalpa.pdf
25. Donaldson LJ, Kelley ET, Dhingra-Kumar N, et al. Medication Without Harm: WHO's Third Global Patient Safety Challenge. Lancet (London, England) 2017;389:1680–1. doi:10.1016/S0140-6736(17)31047-4
26. Aitken M, Gorokhovich L. Advancing the Responsible Use of Medicines: Applying Levers for Change. SSRN Electron J Published Online First: 17 September 2012. doi:10.2139/ssrn.2222541
27. Institute of Medicine. Preventing Medication Errors. Washington: The National Academic Press 2007.
28. Feigenbaum P, Neuwirth E, Trowbridge L, et al. Factors Contributing to All-cause 30-day Readmissions. Med Care 2012;50:599–605. doi:10.1097/MLR.0b013e318249ce72
29. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects—advantages and disadvantages. Nat Clin Pract Rheumatol 2007;3:725–32. doi:10.1038/ncprheum0652
30. Hashimoto RE, Brodt ED, Skelly AC, et al. Administrative database studies: goldmine or goose chase? Evid Based Spine Care J 2014;5:74–6. doi:10.1055/s-0034-1390027
31. Statistics Canada. Population estimates on July 1st, by age and sex. 2018. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501 (accessed 25 May 2019).
32. Schultz SE, Rothwell DM, Chen Z, et al. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. Chronic

Dis Inj Can 2013;33:160–6.http://www.ncbi.nlm.nih.gov/pubmed/23735455 (accessed 17 May 2019).
33. Jaakkimainen RL, Bronskill SE, Tierney MC, *et al.* Identification of Physician-Diagnosed Alzheimer's Disease and Related Dementias in Population-Based Administrative Data: A Validation Study Using Family Physicians' Electronic Medical Records. *J Alzheimer's Dis* 2016;54:337–49. doi:10.3233/JAD-160105
34. Hux JE, Ivis F, Flintoft V, *et al.* Diabetes in Ontario: Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25:512–6. doi:10.2337/diacare.25.3.512
35. Tu K, Chen Z, Lipscombe LL, et al. Prevalence and incidence of hypertension from 1995 to 2005: a population-based study. CMAJ 2008;178:1429–35. doi:10.1503/cmaj.071283
36. Tu K, Campbell NR, Chen Z-L, et al. Accuracy of administrative databases in identifying patients with hypertension. Open Med 2007;1:e18-26.http://www.ncbi.nlm.nih.gov/pubmed/20101286 (accessed 17 May 2019).
37. Tanuseputro P, Budhwani S, Bai YQ, et al. Palliative care delivery across health sectors: A population-level observational study. Palliat Med 2017;31:247–57. doi:10.1177/0269216316653524
38. Steinberg BA, Greiner MA, Hammill BG, et al. Contraindications to Anticoagulation Therapy and Eligibility for Novel Anticoagulants in Older Patients with Atrial Fibrillation. Cardiovasc Ther 2015;33:177–83. doi:10.1111/1755-5922.12129
39. Decousus H, Tapson VF, Bergmann J-F, et al. Factors at Admission Associated With Bleeding Risk in Medical Patients. Chest 2011;139:69–79. doi:10.1378/chest.09-3081
40. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv 2018;2:3198–225. doi:10.1182/bloodadvances.2018022954
41. MHASEF Research Team. Mental Health and Addictions System Performance in Ontario: A Baseline Scorecard. Toronto: 2018.
42. Wells G, Coyle D, Cameron C, et al. Safety, Effectiveness, and Cost-Effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation. Canadian Agency for Drugs and Technologies in Health 2012. http://www.ncbi.nlm.nih.gov/pubmed/24279001 (accessed 22 Jul 2019).
43. Linden CMJ van der, Jansen PAF, Geerenstein EV van, et al. Reasons for Discontinuation of Medication During Hospitalization and Documentation Thereof: A Descriptive Study of 400 Geriatric and Internal Medicine Patients. Arch Intern Med 2010;170:1081. doi:10.1001/archinternmed.2010.159
44. Viktil KK, Blix HS, Eek AK, et al. How are drug regimen changes during hospitalisation handled after discharge: a cohort study. BMJ Open 2012;2:e001461. doi:10.1136/BMJOPEN-2012-001461
45. Little D, Chai-Adisaksopha C, Hillis C, et al. Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis. Thromb Res 2019;175:102–9. doi:10.1016/j.thromres.2019.01.020
46. Levy AR, O'Brien BJ, Sellors C, et al. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2003;10:67–71.http://www.ncbi.nlm.nih.gov/pubmed/12879144 (accessed 16 May 2019).

47. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009;361:1139–51. doi:10.1056/NEJMoa0905561
48. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med 2011;365:883–91. doi:10.1056/NEJMoa1009638
49. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2011;365:981–92. doi:10.1056/NEJMoa1107039
50. Varadhan R, Weiss CO, Segal JB, et al. Evaluating Health Outcomes in the Presence of Competing Risks. Med Care 2010;48:S96–105. doi:10.1097/MLR.0b013e3181d99107
51. Andersen PK, Geskus RB, de Witte T, et al. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;41:861–70. doi:10.1093/ije/dyr213
52. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. Pharmacoepidemiol Drug Saf 2012;21:154–62. doi:10.1002/pds.2341
53. Sanfilippo KM, Wang T-F, Gage BF, et al. Improving accuracy of International Classification of Diseases codes for venous thromboembolism in administrative data. Thromb Res 2015;135:616–20. doi:10.1016/j.thromres.2015.01.012
54. Arnason T, Wells PS, van Walraven C, et al. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. Thromb Res 2006;118:253–62. doi:10.1016/j.thromres.2005.06.015
55. White RH, Garcia M, Sadeghi B, et al. Evaluation of the predictive value of ICD-9-CM coded administrative data for venous thromboembolism in the United States. Thromb Res 2010;126:61–7. doi:10.1016/j.thromres.2010.03.009
56. Birman-Deych E, Waterman AD, Yan Y, et al. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43:480–5.http://www.ncbi.nlm.nih.gov/pubmed/15838413 (accessed 24 Jun 2019)
57. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res 2008;43:1424–41.http://www.ncbi.nlm.nih.gov/pubmed/18756617 (accessed 16 May 2019).
58. Juurlink D, Preyra C, Croxford R, et al. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: 2006. https://www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information (accessed 28 May 2019).
59. Quan H, Li B, Couris CM, et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. Am J Epidemiol 2011;173:676–82. doi:10.1093/aje/kwq433
60. Pisters R, Lane DA, Nieuwlaat R, et al. A Novel User-Friendly Score (HAS-BLED) To Assess 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation. Chest 2010;138:1093–100. doi:10.1378/chest.10-0134
61. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124–d124. doi:10.1136/bmj.d124
62. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative Management of Antithrombotic Therapy. Chest 2012;141:e326S-e350S. doi:10.1378/chest.11-2298
63. Adam SS, McDuffie JR, Ortel TL, et al. Comparative Effectiveness of Warfarin and New Oral Anticoagulants for the Management of Atrial Fibrillation and Venous

Thromboembolism. Ann Intern Med 2012;157:796. doi:10.7326/0003-4819-157-10-201211200-00532
64. Hinojar R, Jiménez-Natcher JJ, Fernández-Golfín C, et al. New oral anticoagulants: a practical guide for physicians. Eur Hear J - Cardiovasc Pharmacother 2015;1:134–45. doi:10.1093/ehjcvp/pvv002
65. Vranckx P, Valgimigli M, Heidbuchel H. The Significance of Drug-Drug and Drug-Food Interactions of Oral Anticoagulation. Arrhythmia Electrophysiol Rev 2018;7:55–61. doi:10.15420/aer.2017.50.1
66. Sayani S, Iqbal O, Hoppensteadt D, et al. Drug Interactions of Newer Oral Anticoagulants Dabigatran, Rivaroxaban, and Apixaban with Routinely Used Nonanticoagulant/Antiplatelet Drugs. Blood 2014;124.
67. Liu A, Abrahamowicz M, Siemiatycki J. Conditions for confounding of interactions. Pharmacoepidemiol Drug Saf 2016;25:287–96. doi:10.1002/pds.3924
68. Health Quality Ontario. Quality in Primary Care: Setting a foundation for monitoring and reporting in Ontario. Toronto: 2015.
69. Lapointe-Shaw L, Mamdani M, Luo J, et al. Effectiveness of a financial incentive to physicians for timely follow-up after hospital discharge: a population-based time series analysis. CMAJ 2017;189:E1224–9. doi:10.1503/cmaj.170092
70. van Walraven C, Mamdani M, Fang J, et al. Continuity of care and patient outcomes after hospital discharge. J Gen Intern Med 2004;19:624–31. doi:10.1111/j.1525-1497.2004.30082.x
71. Williams JI and Young W, A Summary of Studies on the Quality of Health Care Administrative Databases in Canada. In Goel V, Williams JI, Anderson GM, Blackstien-Hirsch P, Fooks C, Naylor CD (eds). Patterns of Health Care in Ontario, The ICES Practice Atlas. 2nd edition. Ottawa: Canadian Medical Association, 1996:339-345.
72. Kyriacou DN, Lewis RJ. Confounding by Indication in Clinical Research. JAMA 2016;316:1818. doi:10.1001/jama.2016.16435
73. Csizmadi I, Collet J-P, Boivin J-F. Bias and Confounding in Pharmacoepidemiology. In: Pharmacoepidemiology. Chichester, UK: : John Wiley & Sons, Ltd 791–809. doi:10.1002/9780470059876.ch47
74. Austin PC, Mamdani MM, van Walraven C, et al. Quantifying the impact of survivor treatment bias in observational studies. J Eval Clin Pract 2006;12:601–12. doi:10.1111/j.1365-2753.2005.00624.x
75. Ogundimu EO, Altman DG, Collins GS. Adequate sample size for developing prediction models is not simply related to events per variable. J Clin Epidemiol 2016;76:175–82. doi:10.1016/j.jclinepi.2016.02.031
76. Faraway JJ. Does data splitting improve prediction? Stat Comput 2016;26:49–60. doi:10.1007/s11222-014-9522-9
77. Picard RR, Berk KN. Data Splitting. Am Stat 1990;44:140. doi:10.2307/2684155
78. Royston P, Moons KGM, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. BMJ 2009;338:b604. doi:10.1136/bmj.b604
79. Derksen S, Keselman HJ. Backward, forward and stepwise automated subset selection algorithms: Frequency of obtaining authentic and noise variables. Br J Math Stat Psychol 1992;45:265–82. doi:10.1111/j.2044-8317.1992.tb00992.x
80. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat

Med 1996;15:361–87. doi:10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4

81. Uchino K, Hernandez A V. Dabigatran Association With Higher Risk of Acute Coronary Events. Arch Intern Med 2012;172:397. doi:10.1001/archinternmed.2011.1666
82. Clemens A, Fraessdorf M, Friedman J. Cardiovascular outcomes during treatment with dabigatran: comprehensive analysis of individual subject data by treatment. Vasc Health Risk Manag 2013;9:599–615. doi:10.2147/VHRM.S49830
83. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation 2016;133:601–9. doi:10.1161/CIRCULATIONAHA.115.017719

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-13
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-17
		(*b*) Describe any methods used to examine subgroups and interactions	16
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	16
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A

Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.