PREDICTORS OF ORAL ANTICOAGULANT-ASSOCIATED ADVERSE EVENTS

PREDICTORS OF ORAL ANTICOAGULANT-ASSOCIATED ADVERSE EVENTS IN SENIORS TRANSITIONING FROM HOSPITAL TO HOME: A RETROSPECTIVE COHORT STUDY

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TITLE: Predictors of Oral Anticoagulant-associated Adverse Events in Seniors Transitioning from Hospital to Home
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Lay Abstract (150 words)

Background
Oral anticoagulants (OACs) are associated with serious adverse events, with high rates immediately post-hospitalization. We aimed to identify and validate clinical and continuity of care variables in seniors discharged from hospital on an OAC, which are associated with OAC-related harm in the short-term high-risk period following hospitalization.

Methods
Data from administrative health databases in Ontario were used to identify and validate risk factors associated with time to first OAC-related serious events including hospitalization or emergency department visit for a bleeding or thromboembolic event, and mortality. Cox proportional hazards model and split sample methods were utilized.

Results
We included 120,721 seniors of which 5423 suffered one of the primary events. Patient-, physician- and index hospitalization-characteristics were all associated with time to composite outcome. Though continuity of care risk factor was part of the final model, it was not a significant predictor for the outcome.

Conclusion
Exploration of this model through sensitivity analysis is required.

ABSTRACT (270 words)

Background
Our objective was to identify and validate clinical and continuity of care variables associated with Oral anticoagulant (OAC)-related adverse events within 30 days of hospital discharge amongst seniors.

Methods and Analysis
This was a population-based retrospective cohort study of all adults aged 66 years or older who were discharged from hospital on an OAC from September 2010 to March 2015 in Ontario, Canada. The primary outcome was a composite of the time to 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 was used to determine the association between the composite outcome and a set of prespecified covariates. A split sample method was applied to validate the final model.

Results
We included 120 721 Ontario seniors of which 5423 suffered one of the primary adverse events. Patients discharged on a direct acting oral anticoagulant (DOAC); dispensed the same OAC in the past 12 months; who had a history of a thromboembolic event; had a recent joint replacement or major surgery; had a cardiologist, hematologist or orthopedic surgeon as compared to a family medicine physician as the physician prescribing the OAC at discharge had a lower risk for the composite outcome. Though continuity of care was a variable in the final multivariate Cox model, it was not significant. The Cox model was stable with acceptable discrimination but poor goodness-of-fit.

Conclusion
In this study, we found that continuity of care as measured by outpatient follow-up in the 7 days post discharge was not significantly associated with the composite outcome. Further exploration to improve the current model's calibration and interpretation are required.

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TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

AF	Atrial Fibrillation
CI	Confidence Intervals
DOAC	Direct-acting Oral anticoagulants
ED	Emergency Department
HR	Hazard Ratios
ICES	Institute for Clinical Evaluative Sciences
OAC	Oral anticoagulants
PH	Proportional Hazards
SD	Standard Deviation
VTE	Venous Thromboembolism

DECELARATION OF ACADEMIC ACHIEVEMENT

I, Harsukh Benipal, declare this thesis entitled, “Predictors of Oral Anticoagulant-associated Adverse Events in Seniors Transitioning from Hospital to Home” to be my own work, submitted for the degree of Masters of Science (M.S.c) to McMaster University. I completed this work between September 2017 and August 2019. I am the sole author of this document and no part of this work has been submitted or published elsewhere.

To the best of my knowledge, the contents of this thesis do not infringe upon any copyrights.

My supervisor, Dr. Anne Holbrook, and my supervisory committee, which comprises of Dr. James Douketis, Dr. Lehana Thabane, and Gary Foster have provided their guidance and support throughout my graduate studies. I carried out all the primary analyses and wrote this entire document myself.

CHAPTER 1: Introduction – Establishing the context

1.0 ORAL ANTICOAGULANTS

Oral anticoagulants (OACs) are widely prescribed for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF) and for the treatment and secondary prevention of venous thromboembolism (VTE) [1-3]. The choice of anticoagulant drug was expanded following the approval of direct acting oral anticoagulants (DOACs), including dabigatran, rivaroxaban and apixaban as alternatives to dose-adjusted warfarin, by Health Canada [4-6]. Though highly effective, warfarin has a narrow therapeutic index, requiring frequent monitoring, and has drug, food and disease state interactions [7]. However, DOACs have higher drug costs, require monitoring of renal function, and have drug and disease interactions that are yet to be fully clarified [7].

Following the approval of DOACs in Canada, the total number of annual OAC prescriptions dispensed increased from about 4.8 to 7 million between 2008-2013 [8]. The proportion of warfarin prescription during this time fell from 99% in 2010 to 67% in 2014, once DOACs began to be recommended for limited access on public plan formularies. [8-11].

1.1 ORAL ANTICOAGULANTS-RELATED HARM

Despite the introduction of DOACs, which are associated with less bleeding, OACs remain one of the top drug families associated with serious adverse events, primarily resulting from bleeding and thromboembolic event [12,13]. It is estimated that annually in the United States about 8.2% of warfarin users experience adverse drug events [14]. A systematic review and meta-analysis of RCTs with OAC treatment lasting 3 to 24 months, reported a 4.3% rate of major bleeding, defined as major bleeding by the included studies or as defined by the International Society on Thrombosis and Haemostasis (fatal bleeding symptomatic bleeding in a

critical area or organ, or bleeding cause a fall in hemoglobin level of 20 g/L or more or leading to transfusion of two or more units of whole blood or red cells), and a 27.2% rate of total bleeding in patients with VTE or AF [15]. A 6.7% rate for all-cause mortality has also been described in a meta-analysis of RCTs, with follow up ranging between 6 to 30 months, for adults using OACs in the treatment of VTE or non-valvular AF [16].

Similarly, population-level studies report high OAC-related adverse events. A study of Ontario seniors discharged from the hospital on an OAC reported a bleeding rate of 26.4% (95% confidence interval [CI] 25.3-27.4) per person-year, and thromboembolic event rate of 32.4% (95% CI 31.3-33.5) per person-year within the first 30-days post-discharge [17]. High bleeding event rates, 11.8% per person-year, were also reported amongst Ontario seniors with AF during the first 30 days of initiating warfarin therapy [18].

It is estimated that OACs are implicated in 28% (95% CI 23-32%) and 39% (95% CI 33.7-43.8%) of emergency department (ED) visits for adverse drug events among adults aged 65 to 79 years and those 80 years or older respectively [19].

As such, the Institute of Safe Medication Practise continues to list warfarin and DOACs as high-alert medications, drugs which have a heightened risk of causing significant patient harm when used sub-optimally [13]. Overall, OAC-related adverse events place a burden on patients and healthcare resources especially in the post hospitalization period [14].

1.2 CONCEPTS IN TRANSITIONS OF CARE

Transitions of care occur when patients move from one healthcare setting to another or between healthcare providers [20]. These are vulnerable periods in the provision of healthcare and are associated with increased risk for adverse events and readmissions. A prospective cohort study found that 23% (95% CI 19-28%) of patients discharged from teaching hospitals in Canada

experienced an adverse event within approximately 30 days post-discharge [21]. Of these a majority were adverse drug events (72%) and 12% were preventable or ameliorable [21]. Similarly, an observational study of older adults discharged from teaching hospitals in United Kingdom reported that 37% of patients experienced a medication-related harm within 8 weeks of discharge, of which 52% were potentially preventable [22]. Another Canadian prospective cohort study of community-dwelling patients aged 75 years or older discharged from acute care units at a teaching hospital reported that 31.3% of the patients experienced an adverse event within 6 months following discharge [23]. An observational study reported 18.7% of patients experienced an adverse drug event within 45 days post discharge from hospitals in the United States amongst adults aged 65 years or older, of which 35% were deemed preventable [24]. Transitions out of the hospital are particularly complex processes with heighted risks for patient harm. Thus, management of these transitions needs to be carefully planned so that patients do not suffer harm from errors or delays.

As defined by The American Geriatrics Society, the goals of patient transitions are to ensure coordination and continuity of healthcare [25]. There are several definitions of continuity of care in the literature. The WHO defines continuity of care as "the degree to which a series of discrete health care events are experienced by people as coherent and interconnected over time and consistent with their health needs and preferences" [26]. Continuity of care is thought to be a facilitator of good care coordination as it creates the relationships to support the interactions amongst healthcare teams involved in the management of patients [26].

The literature defines three aspects of continuity of care including informational, relational and management continuity [27]. It has been posited that management continuity is required for both informational and relational continuity [28]. There have been multiple

measures used in the literature to measure these aspects of continuity of care. Particularly the measurement of management continuity is relatively simple in administrative health databases, as it is commonly measured by follow-up visits made following transitions of care [27].

Several studies suggest that prompt medical post-hospitalization follow-up reduces ED visits and hospitalizations among patients with chronic conditions such as congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction and cancer [29-35]. Many clinical practice guidelines recommend physician follow-up within 1-2-weeks post-discharge as best practise to improve continuity of care [36-43]. In the absence of follow up, coordinating medication management post-hospitalization is challenging and is associated with a 28% increases risk of 30-day readmission [44]. As such, in this thesis, outpatient follow-up is used as a surrogate for continuity of care in the post-discharge period.

1.3 KNOWLEDGE GAP

Though effective in managing coagulation disorders, optimal use of anticoagulants requires a comprehensive approach to patient management [45]. High rates of OAC-related adverse events in the early post-discharge period suggest an opportunity to improve patient outcomes by bettering continuity of care for OAC users during this transition period [14,46]. Identification of continuity of care and clinical risk factors, associated with adverse events amongst older users of OACs may inform prescribing decisions and help identify patients at higher risk of complications, who might benefit from intervention in the early post-discharge period.

Clinical scores including the CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category), which predicts thromboembolic events in patients for AF, and HAS-BLED (Hypertension,

Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly), which predicts hemorrhage in anticoagulated patients, have been developed and validated in multiple patient populations as clinical decision support tools to support initiation of anticoagulation based on stroke and bleeding risk amongst patients with AF or VTE [47-49]. These scores are not derived to predict the combined OAC-related adverse events including hospitalization or ED visits for hemorrhage or thromboembolic events, and mortality in a heterogeneous population of senior OAC users.

Overall, this thesis will fulfill a crucial gap in the literature, by identifying important risk factors, both clinical and continuity of care, predicting OAC-related adverse events in the short-term period following hospitalization. Specifically, these validated continuity of care and clinical risk factors may be useful targets for future intervention trials.

1.4 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 service within 7 days of discharge, will be associated with lower risk for the composite outcome in the 30 days following hospitalization.

1.5 METHODOLOGY

Administrative Healthcare Databases

Administrative health data has been widely used to conduct pharmacoepidemiology drug safety and efficacy studies. In Ontario, health information including provision of physician services, drug use by the elderly and hospital services are collected. ICES is the entity which manages this data in Ontario, taking necessary precautions to ensure anonymity and privacy of all linked administrative data. For this thesis, several administrative databases, including those with information on the patient's demographics, comorbidities, health services and medications provisioned to the patient, healthcare providers and facilities involved with the care of the patient, were linked together using unique patient identifiers.

There are advantages and challenges when using administrative health databases. Firstly, using population-based data minimizes selection bias as all eligible patients receiving routine medical care in the province can be included in the study [50]. However, observational studies are susceptible to bias and confounding which can make results difficult to interpret [50]. For this reason, observational studies cannot be used to measure causal effects of treatments.

A common challenge in conducting pharmacoepidemiology studies using administrative health data results from confounding by indication and by severity of illness [51]. This is unavoidable as prescribing intentionally and rationally is a pillar of good medical practise. Though use of analytic techniques including multivariable regression modelling is recommended to deal with confounding, administrative health databases are limited in clinical detail and thus residual confounding may remain [52]. Despite these challenges, ease and low costs associated with use of administrative health databases to conduct observational studies has produced

meaningful results for hypothesis generation and to inform the design of clinical trials [52]. As such, in this thesis a cohort study using administrative health data is conducted.

Survival Analysis

In survival analysis, the outcome of interest is both whether an event occurred and the time to the event occurrence following the start of the observation period [53]. Survival analysis examines time to event outcome. These methods are used to study the distribution of survival times across multiple treatment arms and can be used to explore the relationship between explanatory variable and survival time. Survival analysis methods, including the Cox Proportional Hazards Model, are developed to use all available data for patients even when right censoring is present [54]. Right censoring occurs when individuals have either been lost to follow up or have survived until the end of the observation period [55]. Additionally, survival data are rarely normally distributed rather are skewed and comprise of many early events and few late events [55]. These features can be explored via survival analysis methods and thus are the methods used to complete the current thesis.

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CHAPTER 2: Predictors of Oral Anticoagulant-associated Adverse Events in Seniors Transitioning from Hospital to Home: A Retrospective Cohort Study Protocol

2.0 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.

2.1 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 high event rates especially in the early post-discharge 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].

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.

2.2 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 [25,26].

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 [27].

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 [28-32]. 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 [50]; Ontario Dementia Database (DEMENTIA) [51]; Ontario Diabetes

	Database (ODD) [52]; Ontario Hypertension Dataset (HYPER) [53,54]
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 [33].

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 [34,35].

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 [36]. 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 [37].

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 [38-42].

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 [43-47]. 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 [45].

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 [48,49].

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 [50].

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 [51-53]; therefore, comorbidities including dementia and diabetes will be captured [29,30]. In addition, patients with a history of substance or alcohol abuse in the past 3 years prior to cohort entry will be identified [54]. 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 [55]. 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 [56]. 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 [57]. 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 [58-60]. 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 [60-62]. 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 [63,64]. 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 [65].

Quality checks

Data are unlikely to be missing at random [37,49,66]. For categorical variables an additional 'missing' category will be included. If $\geq$ 10% of observations are missing multiple imputations are planned.

Bias

Bias in pharmacoepidemiology studies results from multiple sources of confounding [63,67,68]. DOAC users tend to be younger with fewer comorbidities than warfarin users [69]. 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 [70]. 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 [71]. 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 also will 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	**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 [72]. 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 [73]. 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 [74]. The effect of multicollinearity between predictors would inflate the values of the standard errors of the coefficients in the model, which may drive some predictors away from statistical significance. 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 importance.

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 [75]. 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 [76].

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 or DOACs is associated with an increased risk of acute myocardial infarction [77,78], while other meta-analyses have not identified an increased risk for dabigatran or DOACs [79-81]. Observational cohort studies have also been inconclusive with one identifying a two-fold higher risk of acute myocardial infarction in users of dabigatran and rivaroxaban as compared to vitamin K antagonists, while another reported significant risk reduction in acute myocardial infarction for apixaban, rivaroxaban, dabigatran users, as compared with vitamin K antagonists in patients with AF [82,83]. Given that the evidence on risk for acute myocardial infarction in OAC users is inconclusive, a sensitivity analysis with this event in the definition of the composite outcome will be performed using the aforementioned methods.

Moreover, to investigate whether the predictors persist after treating all-cause death, as a competing risk for hemorrhagic and thromboembolic events, we will perform a competing risk analysis. A cause-specific Cox proportional hazards model will be constructed [84]. 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 [93]. 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 [76]. Discrimination will be evaluated using Harell's C-index representing the area under the receiver operating characteristic curve with larger values indicating better discrimination [76].

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.

2.3 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.

2.4 AUTHORS 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.

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2.6 REFERENCES

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CHAPTER 3: Predictors of Oral Anticoagulant Associated Adverse Events in Seniors Transitioning from Hospital to Home- Results Paper

3.0 INTRODUCTION

Background and Rationale

Oral anticoagulants (OACs) are commonly prescribed for the prevention and treatment of systemic embolism associated with atrial fibrillation, venous thromboembolism, and stroke [1–3]. There are currently multiple OACs available for commercial use including warfarin and direct-acting oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, and apixaban [4-7]. Despite the introduction of DOACs which require less monitoring and have demonstrated reduced bleeding in large randomized controlled trials, OACs remain one of the top drug families associated with serious adverse events, primarily due to bleeding and thromboembolic events [8,9].

Hospitalization has been previously reported to be associated with worse anticoagulation control, proportion of days in therapeutic range, in elderly patients treated with warfarin [10]. A population-based study found particularly high rates of bleeding, 26.4% (95% confidence interval [CI] 25.3-27.4) per person-year, and thromboembolic events, 32.4% (95% CI 31.3-33.5) per person-year, in elderly OAC users within the first 30-days after hospital discharge [11]. The same cohort of senior OAC users will be used in the current thesis.

Several studies suggest that prompt primary care follow-up post-hospitalization reduces emergency department (ED) visits and hospitalizations among patients with chronic conditions [12-18]. High rates of OAC-related adverse events in the early post-discharge period suggest an opportunity to improve patient outcomes by bettering continuity of care for OAC users during their transition out of the hospital [19,20].

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.

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.

3.1 METHODS AND ANALYSIS

Study design and setting

The methods of this study have been described in detail previously (Chapter 2). Briefly, this is a population-based retrospective cohort study in Ontario seniors aged 66 years or older.

Data Sources

The study dataset was created using Ontario's health administrative databases housed at ICES. These databases contain administrative health service records for approximately 14 million Ontarians eligible for the provincial health insurance [21]. These datasets were linked using unique encoded identifiers and analyzed at ICES. Please refer to the protocol (Chapter 2) for additional

information on the databases used to identify the study participants, potential risk factors and the outcome variable.

Observation Period

The study's *index date* was defined as the date of OAC dispensing, which had to be within one day of hospital discharge. The patient *accrual period* was September 1, 2010 through March 31, 2015. This large time period allowed for a sufficient sample size to conduct this study.

We defined a 7-day post-discharge blanking period during which patients were dispensed an index OAC, but study outcome events were not measured to avoid survivor-treatment bias [22]. For those who remained in the cohort, outpatient health care contact during the blanking period was recorded. Patients were followed from day 8 to day 30 post-hospitalization (or a maximum follow-up of 24 days). The last *outcome event date* was 30 April 2015. Patients were censored at a hospitalization lasting more than 5 days, since information on in-hospital medications are not available in administrative claims data and medications are often changed or discontinued during hospital admission [23,24].

Participants

Inclusion and Exclusion Criteria

The source population was Ontario residents aged 66 years or older who were 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, were excluded, as resumption in OAC therapy after a bleeding event is associated with an increased risk for recurrent

bleeds [25]. All patients who experienced the composite event in the 7 days blanking period were excluded.

Variables

Outcomes

The primary outcome was a composite of time to first hospitalization or ED visit for a hemorrhage or thromboembolic event, or death from any cause. These events are common serious OAC-associated adverse events. Including death avoided the problem of competing risks [26,27].

Comprehensive definitions and data sources used to identify the composite event can be found in the study protocol (Chapter 2). Thromboembolic events included both venous and arterial events. Hemorrhagic events included intracranial bleeds, upper and lower gastrointestinal bleeds, and any other bleeds which required a hospital admission or a visit to an ED. International Classification of Diseases (ICD) 10th revision diagnosis codes and Canadian Classification of Health Interventions procedure codes were used to identify these conditions in the administrative health databases [28-34].

Risk Factors

The full list of clinical and continuity of care risk factors being explored in this project, as well as their data sources, are located in Chapter 2. In brief, patient demographic characteristics captured as of the date of cohort entry included age, sex, socioeconomic status (as defined by census neighborhood income quintiles), rural residence, receipt of palliative care, and whether the patient was rostered with a primary care physician were included.

Characteristics of the index hospitalization including type of hospital, length of index hospitalization and type of discharge were captured. We also captured specialty of the physician responsible for index OAC prescription and OAC dispensed at index prescription date. The cohort

was categorized into three categories of OAC users including incident (patients who were not dispensed an OAC in the year prior to cohort entry), prevalent non-switchers (patients who were dispensed the same OAC in the year prior to cohort entry) and prevalent switchers (patients who were dispensed a different OAC in the year prior to cohort entry).

Existing comorbidities may be associated with outcomes [35-37]; therefore, comorbidities including dementia, diabetes, and active cancer were captured. In addition, patients with a history of substance or alcohol abuse in the past 3 years prior to cohort entry were identified. A diagnosis of obesity, underweight, antiphospholipid syndrome, and delirium were also captured. Hospitalization or ED visits in the 3 years prior to cohort entry for thromboembolic or hemorrhagic events were also recorded.

Several prognostic indices were included. The Deyo-Charlson Comorbidity Index was calculated to describe the cohort [38]. CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category) which predicts thromboembolic events in patients for AF was calculated. HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly) was also calculated which predicts hemorrhage in anticoagulated patients [39,40]. Data on labile international normalized ratio were not available or relevant for most of our patient, so we calculated the HAS-B_ED score.

Indications that result in the prescription of OACs were recorded to control for confounding by indication including presence of atrial fibrillation (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

(excluding same day surgery) during index hospitalization, presence of a mechanical heart valve, and deep vein thrombosis or pulmonary embolism during index hospitalization [41-43].

We also adjusted the model for presence of drug therapies which interact with OACs [44]. As such, use of nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, amiodarone, aspirin, and other antiplatelets in the 120 days prior to cohort entry and antibiotic use in the 30 days prior to cohort entry was captured [45-47]. Recent pre-hospital anticoagulant use was also captured.

Continuity of care was evaluated as a binary variable and considered to occur if there was record of a patient visit within 7 days of discharge by either a primary care physician, nurse practitioner, medical specialist, or a home care service provider including personal support workers or nurses.

Missing data

Data in this type of study are unlikely to be missing at random [48-50]. For categorical variables an additional 'missing' category was included. If there was less than 10% missing data in the cohort no attempts at imputing data were made. However, if $\geq$ 10% of observations were missing multiple imputation were planned.

Bias

Bias in pharmacoepidemiology studies results from multiple sources of confounding [47,51,52]. To control for confounding, we included variables such as age, sex, presence of specific comorbidities, potential drug-drug interactions, remote residence, neighbourhood income quintile, and physician specialty amongst other independent variables in the model as potential risk factors.

Sample Size

For Cox regression, a fitted model is likely to be reliable and stable when the number of participants with the outcome is 20 times the number of covariates [53]. We anticipated up to 30 covariates to be included in the final multivariate Cox regression model; therefore, a minimum of 600 patients (30 covariates x 20) with the composite event were required to devise the models.

Statistical Plan

All data was examined descriptively. Given that the primary outcome was a time-to-event outcome, Cox proportional hazards model was used to determine the association between the composite outcome and all risk factors.

Model Construction

Model derivation and validation were based on a split-sample method [54]. Two-thirds of the study participants were randomly assigned to a model derivation cohort, and one-third was reserved as an independent validation cohort [55].

The model was developed based on data from the derivation cohort alone. Given that highly correlated risk factors add little independent information to the model, tolerance statistic of below 0.1 and a variance inflation factor of above 10 were used to identify multicollinearity. If multicollinearity was present, one of the highly correlated predictors was removed.

Subsequently, univariate Cox regression models were developed to select variables, with p-value less than or equal to 0.20, for entry into the multivariable Cox regression model. Given the exploratory nature of this study, a backward stepwise approach was used for selection of risk factors for inclusion of variables in the final multivariate Cox model [56]. Least significant independent variables were removed until all p-values were below 0.2. The proportionality

assumption was assessed using Schonfeld residuals and Log of negative log of estimates survivor function graphs [57].

Model Validation

Once the final model was developed, it was assessed in the separate validation cohort of patients. The predictive accuracy of the model was assessed using tests for discrimination and calibration [57]. We evaluated the model's calibration by conducting a simplified overall goodness-of-fit test which is algebraically identical to Gronnesby and Borgan test. This simplified goodness-of-fit test relies on calculation of score tests available in any statistical software package, where a significant p-value eluded to potential problems in model performance [58]. Discrimination was evaluated using Harell's c-index representing the area under the receiver operating characteristic curve with larger values, highest being a value of 1, indicating better discrimination [57].

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

3.2 RESULTS

Patient Characteristics

Over the 5-year accrual period, 120 721 Ontario seniors, aged 66 years or older, who had been dispensed an OAC within one day of hospital discharge were identified (Figure 1). There was very little missing data in the cohort. 66 patients' residence information and 557 patients' income information was missing. 1282 (1.1%) of patients in the cohort were missing the type of hospital institution (teaching, community or small) from which they were discharged.

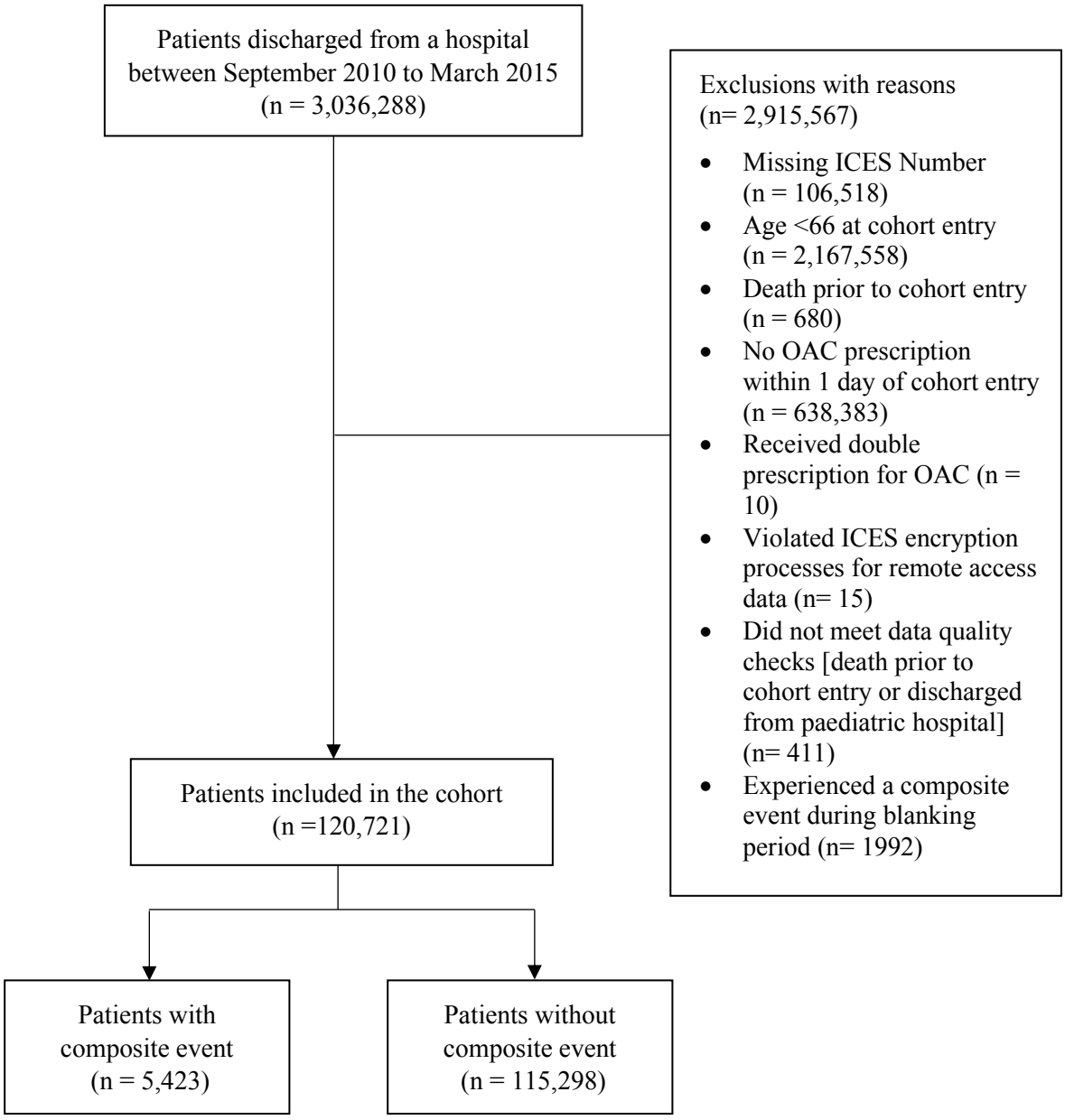

Figure 1. Cohort selection diagram. Note: OAC= Oral anticoagulants

The included patients' demographic and clinical characteristics are reported in Table 1. Briefly, of the included patients, 71,783 (59.5%) were aged 75 years or older and 67,172 (55.6%) were female. 69,3112 (57.4%) of the cohort was enrolled in a primary care practise, team or with a primary care physician at the time of index hospitalization. There were 4515 (n= 3.7%) palliative

patients identified in the cohort. The mean CHA_2DS_2-VASc and HAS-B_ED scores at the start of observation period were 4.1 (Standard Deviation [SD]: 1.6) and 2.2 (SD: 0.7), respectively. 72,574 patients (60.1%), had received follow up without an event, from primary care physicians, medical specialists, nurse practitioners or homecare services, between day 0 and day 7 post index-hospitalization.

Incident users, patients who had not been dispensed an OAC in the year prior to cohort entry, made up the majority (57.6%) of the cohort. Warfarin was the most prescribed OAC, at 70.0%, for prevalent users whereas rivaroxaban was the most prescribed OAC, at 61.0%, for incident users at discharge. Orthopedic surgery specialists (40.2%) were the physicians most commonly responsible for OAC prescribing at discharge for incident users. Family medicine physicians (54.1%) were responsible for most OAC prescriptions to prevalent users. The main indication for OAC use was AF (76.1%) and joint replacement (55.9%) amongst prevalent and incident users, respectively. The derivation cohort included 80 650 patients while the validation cohort included 40 071 patients, and both cohorts had a median follow-up of 30 days following hospital discharge. Characteristics of the derivation and validation cohort are reported in Table 1.

Outcomes

The total person-time spent in follow-up observation period was 3,525,934 days. Event rates among the cohort are reported in Table 2. There were 5423 composite events, 1546 (1.3%) hospitalizations or ED visits for a hemorrhage, 950 (0.8%) for a thromboembolic event and 2927 (2.4%) deaths, between day 8 to day 30. The incidence of the composite outcome was higher amongst the prevalent users at 7.0% (n= 3622) as compared to incident users at 2.6% (n= 1801). Death was the most common event at 2.4% (n= 2927) in the entire cohort, 4.5% amongst the prevalent OAC users, and 0.9% amongst the incident OAC users. Between day 8 to day 30

hospitalization or ED visits due to hemorrhagic events occurred for 1.3% of the patients while thromboembolic events occurred for 0.8% of the patients.

Table 6: Characteristics of study participants in the entire cohort, including in the derivation and validation cohort.

Baseline Characteristic	**Total**					**Derivation Cohort**	**Validation Cohort**
		Incident Users	**Prevalent Users**	**Patients with a composite event**	**Patients without a composite event**	**Total**	**Total**
	no. (%)						
	n= 120,721	**n=69,253 (57.6%)**	**n= 51,468 (42.8%)**	**n=5,423**	**n= 115,298**	**n= 80,650**	**n= 40,071**
Age category, yr							
66-75	48938 (40.5%)	35710 (51.6%)	13228 (25.7%)	1168 (21.5%)	47770 (41.4%)	32567 (40.4%)	16371 (40.8%)
76-85	48194 (39.9%)	25901 (37.4%)	22293 (43.3%)	2273 (41.9%)	45921 (39.8%)	32234 (40.0%)	15960 (39.8%)
≥ 86	23589 (19.5%)	7642 (11.0%)	15947 (31.0%)	1982 (36.6%)	21607 (18.7%)	15849 (19.6%)	7740 (19.3%)
Female	67172 (55.6%)	39533 (57.1%)	27639 (53.7%)	2736 (50.4%)	64436 (55.9%)	44820 (55.6%)	22352 (55.8%)
Income quintile							
Missing	557 (0.5%)	254 (0.4%)	303 (0.6%)	33 (0.6%)	524 (0.4%)	373 (0.5%)	184 (0.4%)
1	22822 (18.9%)	11963 (17.3%)	10859 (21.1%)	1195 (22.0%)	21627 (18.8%)	15244 (18.9%)	7578 (18.9%)
2	24190 (20.0%)	13609 (19.6%)	10581 (20.6%)	1144 (21.1%)	23046 (20.0%)	16280 (20.2%)	7910 (19.7%)
3	24172 (20.0%)	13937 (20.1%)	10235 (19.9%)	1057 (19.5%)	23115 (20.0%)	16058 (19.9%)	8114 (20.2%)
4	24629 (20.4%)	14462 (20.9%)	10167 (19.8%)	1007 (18.6%)	23622 (20.5%)	16401 (20.3%)	8228 (20.5%)
5	24351 (20.2%)	15028 (21.7%)	9323 (18.1%)	987 (18.2%)	23364 (20.3%)	16294 (20.2%)	8057 (20.1%)
Rural Residence							
Missing	66 (0.1%)	44 (0.1%)	22 (0.0%)	<6 (<0.1%)*	63 (0.1%)	50 (0.1%)	16 (0.0%)

Yes	19505 (16.2%)	11701 (16.9%)	7804 15.2%)	828 (15.3%)	18677 (16.2%)	13143 (16.3%)	6362 (15.9%)
No	101150 (84.2%)	57508 (83.0%)	43642 (84.8%)	4592 (84.7%)	96558 (83.7%)	67457 (83.6%)	33693 (84.1%)
Rostered with a primary care practice, physician or team	69312 (57.4%)	35303 (51.0%)	34009 (66.1%)	3933 (72.5%)	65379 (56.7%)	46392 (57.5%)	22920 (57.2%)
Palliative patient	4514 (3.7%)	1107 (1.6%)	3407 (6.6%)	767 (14.1%)	3747 (3.2%)	3032 (3.8%)	1482 (3.7%)
Type of hospital from which patient was discharged							
Teaching	29494 (24.6%)	16576 (23.9%)	12918 (25.1%)	1297 (23.9%)	28197 (24.5%)	19719 (24.4%)	9775 (24.4%)
Community	85703 (71.3%)	50315 (72.7%)	35388 (68.8%)	3812 (70.3%)	81891 (71.0%)	57254 (80.0%)	28449 (71.0%)
Small	4242 (3.5%)	1665 (2.4%)	2577 (5.0%)	268 (4.9%)	3974 (3.5%)	2821 (3.5%)	1421 (3.6%)
Missing	1282 (1.1%)	697 (1.0%)	585 (1.1%)	46 (0.8%)	1236 (1.1%)	856 (1.1%)	426 (1.1%)
Length of index hospitalization, mean (SD)	9.2 (17.4)	7.4 (14.9)	11.6 (20.1)	13.0 (18.5)	9.0 (17.4)	9.2 (17.4)	9.2 (17.5)
Median (IQR)	5 (3-9)	4 (3-7)	7 (4-12)	8 (4-15)	5 (3-9)	5 (3-9)	5 (3-9)
Physician specialty responsible for index OAC prescription							
Family Medicine	40119 (33.2%)	12291 (17.8%)	27828 (54.1%)	3101 (57.2%)	37018 (32.1%)	26863 (33.3%)	13256 (33.1%)
Cardiologist	6969 (5.8%)	3777 (5.4%)	3192 (6.2%)	299 (5.5%)	6670 (5.8%)	4735 (5.9%)	2234 (5.6%)
Hematologist	2291 (1.9%)	1785 (2.6%)	506 (1.0%)	67 (1.2%)	2224 (1.9%)	1505 (1.9%)	786 (2.0%)
Internal Medicine	9784 (8.1%)	5269 (7.6%)	4515 (8.8%)	493 (9.1%)	9291 (8.1%)	6465 (8.0%)	3319 (8.3%)
Orthopedic Surgery	31211 (25.8%)	27862 (40.2%)	3349 (6.5%)	204 (3.8%)	31007 (26.9%)	20760 (25.7%)	10451 (26.1%)
Oncology	204 (0.2%)	92 (0.1%)	112 (0.2%)	18 (0.3%)	186 (0.2%)	151 (0.2%)	53 (0.1%)
Other Surgery	1985 (1.6%)	1298 (1.9%)	687 (1.3%)	88 (1.6%)	1897 (1.6%)	1343 (1.7%)	642 (1.6%)
Other	28158 (23.3%)	16879 (24.4%)	11279 (21.9%)	1153 (21.3%)	27005 (23.4%)	18828 (23.4%)	9330 (23.3%)

Index OAC prescribed							
Apixaban	5765 (4.8%)	2770 (4.0%)	2995 (5.8%)	285 (5.3%)	5480 (4.8%)	3861 (4.8%)	1904 (4.8%)
Dabigatran	6503 (5.4%)	2748 (4.0 %)	3755 (7.3%)	274 (5.0%)	6229 (5.4%)	4349 (5.4%)	2154 (5.4%)
Rivaroxaban	50940 (42.2%)	42252 (61.0%)	8688 (16.9%)	839 (15.5%)	50101 (43.4%)	33972 (42.1%)	16968 (42.3%)
All DOACs	63208 (52.4%)	47770 (69.0%)	15438 (12.9%)	1398 (25.8%)	61810 (53.6%)	42182 (52.3%)	21026 (52.5%)
Warfarin	57513 (47.6%)	21483 (31.0%)	36030 (70.0%)	4025 (74.2%)	53488 (46.4%)	38468 (47.7%)	19045 (47.5%)
Type of OAC user							
Prevalent	51468 (42.8%)			3622 (66.8%)	47846 (41.5%)	34405 (42.7%)	17063 (42.6%)
Non-switcher	47869 (39.6%)		47869 (93.0%)	3451 (63.6%)	44418 (38.5%)	32000 (39.7%)	15869 (39.6%)
Switcher	3599 (3.0%)		3599 (7.0%)	171 (3.2%)	3428 (3.0%)	2405 (3.0%)	1194 (3.0%)
Incident	69253 (57.6%)			1801 (33.2%)	67452 (58.5%)	46245 (57.3%)	23008 (57.4%)
Type of discharge disposition							
Home	106807 (88.5%)	65839 (95.1%)	40968 (79.6%)	3886 (71.7%)	102921 (89.3%)	71297 (88.4%)	35510 (88.6%)
Long term or continuing care facility	13593 (11.3%)	3296 (4.8%)	10297 (20.0%)	1511 (27.9%)	12082 (10.5%)	9141 (11.3%)	4452 (11.1%)
Other	321 (0.3%)	118 (0.2%)	203 (0.4%)	26 (0.5%)	295 (0.3%)	212 (0.3%)	109 (0.3%)
CHA_2DS_2-VASc Score (components)							
Congestive Heart Failure	45774 (37.9%)	14008 (20.2%)	31766 (61.7%)	3486 (64.3%)	42288 (36.7%)	30685 (38.1%)	15089 (37.7%)
Hypertension	104153 (86.3%)	56719 (81.9%)	47434 (92.2%)	4955 (91.4%)	99198 (86.0%)	69631 (86.3%)	34522 (86.2%)
Age $\geq$ 75 yr	71783 (59.5%)	33543 (48.4%)	38240 (74.3%)	4255 (78.5%)	67528 (58.6%)	48083 (59.6%)	23700 (59.1%)
Diabetes	45486 (37.7%)	22280 (32.2%)	23206 (45.1%)	2487 (45.9%)	42999 (37.3%)	30407 (37.7%)	15079 (37.6%)

Stroke history	9256 (7.7%)	2187 (3.2%)	7069 (13.7%)	710 (13.1%)	8546 (7.4%)	6270 (7.8%)	2986 (7.4%)
Vascular disease	7746 (6.4%)	2367 (3.4%)	5379 (10.4%)	693 (12.8%)	7053 (6.1%)	5185 (6.4%)	2561 (6.4%)
Age ≥ 65 (everyone)	120721 (100%)	69253 (100%)	51468 (100%)	5423 (100%)	115298 (100%)	80650 (100%)	40071 (100%)
Female	67172 (55.6%)	39533 (57.1%)	27639 (53.7%)	2736 (50.4%)	64436 (55.9%)	44820 (55.6%)	22352 (55.8%)
CHA_2DS_2-VASc Score							
1	3684 (3.1%)	3322 (4.8%)	362 (0.7%)	33 (0.6%)	3651 (3.2%)	2495 (3.1%)	1189 (3.0%)
2	14906 (12.4%)	12836 (18.5%)	2070 (4.0%)	186 (3.4%)	14720 (12.8%)	9891 (12.3%)	5015 (12.5%)
3	28977 (24.0%)	22064 (31.9%)	6913 (13.4%)	625 (11.5%)	28352 (24.6%)	19201 (23.8%)	9776 (24.4%)
4	30277 (25.1%)	17158 (24.8%)	13119 (25.5%)	1385 (25.5%)	28892 (25.1%)	20140 (25.0%)	10137 (25.3%)
5	21379 (17.7%)	8402 (12.1%)	12977 (25.2%)	1409 (26.0%)	19970 (17.3%)	14425 (17.9%)	6954 (17.4%)
6	11461 (9.5%)	3396 (4.9%)	8065 (15.7%)	819 (15.1%)	10642 (9.2%)	7733 (9.6%)	3728 (9.3%)
7	6604 (5.5%)	1474 (2.1%)	5130 (10.0%)	593 (10.9%)	6011 (5.2%)	4467 (5.5%)	2137 (5.3%)
8	3121 (2.6%)	557 (0.8%)	2564 (5.0%)	335 (6.2%)	2786 (2.4%)	2087 (2.6%)	1034 (2.6%)
9	312 (0.3%)	44 (0.1%)	268 (0.5%)	38 (0.7%)	274 (0.2%)	211 (0.3%)	101 (0.2%)
HAS-B_ED Score (components)							
Hypertension	104153 (86.3%)	56719 (81.9%)	47434 (92.2%)	4955 (91.4%)	99198 (86.0%)	69631 (86.3%)	34522 (86.2%)
Abnormal renal function	10835 (9.0%)	2438 (3.5%)	8397 (16.3%)	1070 (19.7%)	9765 (8.5%)	7219 (9.0%)	3616 (9.0%)
Abnormal liver function	1306 (1.%)	338 (0.5%)	968 (1.9%)	132 (2.4%)	1174 (1.0%)	872 (1.1%)	434 (1.1%)
Stroke	6530 (5.4%)	1719 (2.5%)	4811 (9.4%)	482 (8.9%)	6048 (5.2%)	4442 (5.5%)	2088 (5.2%)

Bleeding history or predisposition	13022 (10.8%)	3558 (5.1%)	9464 (18.4%)	1101 (20.3%)	11921 (10.3%)	8719 (10.8%)	4303 (10.7%)
Elderly, >65 yr (everyone)	120721 (100%)	69253 (100%)	51468 (100%)	5423 (100%)	115298 (100%)	80650 (100%)	40071 (100%)
Drug consumption	14099 (11.7%)	11557 (16.7%)	2542 (4.9%)	228 (4.2%)	13871 (12.0%)	9408 (11.7%)	4691 (11.7%)
Alcohol abuse in past 3 yr	1357(1.1%)	505 (0.7%)	852 (1.7%)	90 (1.7%)	1267 (1.1%)	928 (1.2%)	429 (1.1%)
HAS-B_ED Score							
1	12663 (10.5%)	9682 (14.0%)	2981 (5.8%)	341 (6.3%)	12322 (10.7%)	8409 (10.4%)	4254 (10.6%)
2	75946 (62.9%)	45021 (65.0%)	30925 (60.1%)	3037 (56.0%)	72909 (63.2%)	50772 (63.0%)	25174 (62.8%)
3	27465 (22.8%)	13463 (19.4%)	14002 (27.2%)	1545 (28.5%)	25920 (22.5%)	18367 (22.8%)	9098 (22.7%)
4	4259 (3.5%)	1017 (1.5%)	3242 (6.3%)	451 (8.3%)	3808 (3.3%)	2852 (3.5%)	1407 (3.5%)
5+	388 (0.3%)	70 (0.1%)	318 (0.6%)	49 (0.9%)	339 (0.3%)	250 (0.3%)	138 (0.3%)
Charlson Comorbidity Index							
0	20657 (17.1%)	11584 (16.7%)	9073 (17.6%)	551 (10.2%)	20106 (17.4%)	13823 (17.1%)	6834 (17.0%)
1	14466 (12.0%)	5963 (8.6%)	8503 (16.5%)	772 (14.2%)	13694 (11.9%)	9714 (12.0%)	4752 (11.9%)
≥ 2	31491 (26.1%)	8773 (12.7%)	22718 (44.1%)	2682 (49.5%)	28809 (25.0%)	21098 (26.2%)	10393 (25.9%)
No hospital admission	54107 (44.8%)	42933 (62.0%)	11174 (21.7%)	1418 (26.2%)	52689 (45.7%)	36015 (44.7%)	18092 (45.2%)
Dementia	18290 (15.2%)	5013 (7.3%)	13277 (25.8%)	1593 (29.4%)	16697 (14.5%)	12326 (15.3%)	5964 (14.9%)
Delirium	5940 (4.9%)	1345 (1.9%)	4595 (8.9%)	545 (10.0%)	5395 (4.7%)	3996 (5.0%)	1944 (4.8%)
No. of hospitalizations (past 1 yr), mean (SD)	0.7 (1.2)	0.3 (0.7)	1.2 (1.4)	1.2 (1.6)	0.6 (1.1)	0.7 (1.2)	0.6 (1.2)
Median (IQR)	0 (0-1)	0 (0-0)	1 (0-2)	1 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)
Atrial fibrillation (past 10 yr)	61357 (50.8%)	22186 (32.0%)	39171 (76.1%)	3961 (73.0%)	57396 (49.8%)	41076 (50.9%)	20281 (50.6%)

Joint replacements (past 35 d)	44091 (36.5%)	38714 (55.9%)	5377 (10.4%)	344 (6.3%)	43747 (37.9%)	29413 (36.5%)	14678 (36.6%)
Major surgery during index hospitalization	21844 (18.1%)	17255 (24.9%)	4589 (8.9%)	408 (7.5%)	21436 (18.6%)	14620 (18.1%)	7224 (18.0%)
Deep vein thrombosis or pulmonary embolism during index hospitalization	5908 (4.9%)	1461 (2.1%)	4447 (8.6%)	838 (15.4%)	5070 (4.4%)	3975 (4.9%)	1933 (4.8%)
Active cancer	7634 (6.3%)	3471 (5.0%)	4163 (8.1%)	652 (12.0%)	6982 (6.1%)	5097 (6.3%)	2537 (6.3%)
Mechanical heart valve	1723 (1.4%)	158 (0.2%)	1565 (3.0%)	148 (2.7%)	1575 (1.4%)	1155 (1.4%)	568 (1.4%)
Anticoagulant (past 120 d)	44339 (36.7%)	132 (0.2%)	44207 (85.9%)	3384 (62.4%)	40955 (35.5%)	29692 (36.8%)	14647 (36.6%)
Medication use (past 120 d)- potentially interacting with OAC use post-discharge							
Amiodarone	3925 (3.2%)	584 (0.8%)	3341 (6.5%)	276 (5.1%)	3649 (3.2%)	2658 (3.3%)	1267 (3.2%)
Non-aspirin Antiplatelet	6857 (5.7%)	4374 (6.3%)	2483 (4.8%)	434 (8.0%)	6423 (5.6%)	4643 (5.8%)	2214 (5.5%)
Aspirin**	2810 (2.3%)	2171 (3.1%)	639 (1.2%)	127 (2.3%)	2683 (2.3%)	1845 (2.3%)	965 (2.4%)
Nonsteroidal Anti-Inflammatory Drugs**	19065 (15.8%)	15215 (22.0%)	3850 (7.5%)	423 (7.8%)	18642 (16.2%)	12747 (15.8%)	6318 (15.8%)
Selective Serotonin Reuptake Inhibitors	14407 (11.9%)	6087 (8.8%)	8320 (16.2%)	911 (16.8%)	13496 (11.7%)	9627 (11.9%)	4780 (11.9%)
Antibiotic use (past 30 d)	16790 (13.9%)	7262 (10.5%)	9528 (18.5%)	1142 (21.1%)	15648 (13.6%)	11200 (13.9%)	5590 (14.0%)
No. of potentially OAC interacting drugs dispensed (past 120 d), mean (SD)	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.6 (0.7)	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)
Median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Comorbidity (past 3 yr)							
Thromboembolic event	21082 (17.5%)	5882 (8.5%)	15200 (29.5%)	1628 (30.0%)	19454 (16.9%)	14215 (17.6%)	6867 (17.1%)
Arterial thromboembolism							
Ischemic stroke	4285 (3.6%)	974 (1.4%)	3311 (6.4%)	333 (6.1%)	3952 (3.4%)	2915 (3.6%)	1370 (3.4%)

Transient Ischemic Stroke (TIA)	2687 (2.2%)	843 (1.2%)	1844 (3.6%)	188 (3.5%)	2499 (2.2%)	1829 (2.3%)	858 (2.1%)
Myocardial Infraction (STEMI or NSTEMI or ACS)	5680 (4.7%)	1782 (2.6%)	3898 (7.6%)	491 (9.0%)	5189 (4.5%)	3774 (4.7%)	1906 (4.8%)
Systemic embolism	687 (0.6%)	151 (0.2%)	536 (1.0%)	57 (1.0%)	630 (0.6%)	472 (0.6%)	215 (0.5%)
Peripheral Vascular Disease event	2454 (2.0%)	668 (1.0%)	1786 (3.5%)	240 (4.4%)	2214 (1.9%)	1668 (2.1%)	786 (2.0%)
Venous thromboembolism							
Pulmonary embolism	2317 (1.9%)	335 (0.5%)	1982 (3.9%)	209 (3.8%)	2108 (1.8%)	1554 (1.9%)	763 (1.9%)
Deep vein thrombosis	3171 (2.6%)	564 (0.8%)	2607 (5.1%)	270 (5.0%)	2901 (2.5%)	2139 (2.6%)	1032 (2.6%)
Hemorrhage event	13022 (10.8%)	3558 (5.1%)	9464 (18.4%)	1101 (20.3%)	11921 (10.3%)	8719 (10.8%)	4303 (10.7%)
Intracranial bleeding	757 (0.6%)	227 (0.3%)	530 (1.0%)	48 (0.9%)	709 (0.6%)	482 (0.6%)	275 (0.7%)
Upper Gastrointestinal bleeding	3739 (3.1%)	1050 (1.5%)	2689 (5.2%)	333 (6.1%)	3406 (3.0%)	2514 (3.1%)	1225 (3.1%)
Lower Gastrointestinal bleeding	1461 (1.2%)	445 (0.6%)	1016 (2.0%)	116 (2.1%)	1345 (1.2%)	1002 (1.2%)	459 (1.2%)
Other major bleeds	8477 (7.0%)	2086 (3.0%)	639 (12.4%)	739 (13.6%)	7738 (6.7%)	5677 (7.0%)	2800 (7.0%)
Overweight or obesity	4286 (3.6%)	2224 (3.2%)	2062 (4.0%)	209 (3.8%)	4077 (3.5%)	2813 (3.5%)	1473 (3.7%)
Underweight	7674 (6.4%)	3335 (4.8%)	4339 (8.4%)	482 (8.9%)	7192 (6.2%)	5159 (6.4%)	2515 (6.3%)
Antiphospholipid syndrome	51 (0.0%)	7 (0.0%)	44 (0.1%)	<6 (<0.1%)*	48 (0.0%)	34 (0.0%)	17 (0.0%)
Substance Abuse	775 (0.6%)	347 (0.5%)	428 (0.8%)	64 (1.2%)	711 (0.6%)	530 (0.7%)	245 (0.6%)
Alcohol Abuse	1348 (1.1%)	521 (0.8%)	827 (1.6%)	85 (1.6%)	1263 (1.1%)	928 (1.2%)	420 (1.1%)
Continuity of Care (within 7d post-hospitalization)							
Follow-up with any relevant outpatient care	72574 (60.1%)	37903 (54.7%)	34671 (67.4%)	3681 (67.9%)	68893 (59.8%)	48406 (60.0%)	24168 (60.3%)
Follow-up with primary care physician	37220 (30.8%)	18429 (26.6%)	18791 (36.5%)	1966 (36.2%)	35254 (30.6%)	24819 (30.8%)	12401 (31.0%)

Follow-up with specialist	7691 (6.4%)	3685 (5.3%)	4006 (7.8%)	386 (7.1%)	7305 (6.3%)	5164 (6.4%)	2527 (6.3%)
Follow-up with home care services	43969 (36.4%)	22891 (33.1%)	21078 (41.0%)	2366 (43.6%)	41603 (36.1%)	29213 (36.2%)	14756 (36.8%)

* suppressed in accordance with ICES' privacy policies.

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

OAC- oral anticoagulant; CHA2DS2-VASc- Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category; HAS-B_ED- Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (excluded), Elderly (>65 years), Drugs/alcohol concomitantly.

Table 7: The outcome events observed within the cohort between day 8 to day 30 including in the derivation and validation cohort.

Outcomes	**Total participants**			**Derivation cohort**	**Validation cohort**
	Total	**Incident users**	**Prevalent users**	**Total**	**Total**
	n= 120,721	n=69,253 (57.6%)	n= 51,468 (42.8%)	n= 80,650	n= 40,071
	n (%)				
Composite event	5423 (4.5%)	1801 (2.6%)	3622 (7.0%)	3669 (4.6%)	1754 (4.4%)
Death	2927 (2.4%)	614 (0.9%)	2313 (4.5%)	2003 (2.5%)	924 (2.3%)
Thromboembolic event	950 (0.8%)	506 (0.7%)	444 (0.9%)	624 (0.8%)	326 (0.8%)
Arterial event					
Ischemic stroke	221 (0.2%)	81 (0.1%)	140 (0.3%)	136 (0.2%)	85 (0.2%)
Transient ischemic attack	93 (0.1%)	42 (0.1%)	51 (0.1%)	61 (0.1%)	32 (0.1%)
Peripheral vascular disease	135 (0.1%)	48 (0.1%)	87 (0.2%)	92 (0.1%)	43 (0.1%)
Systemic embolism	36 (0.0%)	21 (0.0%)	15 (0.0%)	19 (0.0%)	17 (0.0%)
Venous event					
Pulmonary embolism	199 (0.2%)	143 (0.2%)	56 (0.1%)	133 (0.2%)	66 (0.2%)
Deep vein thrombosis	266 (0.2%)	171 (0.2%)	95 (0.2%)	183 (0.2%)	83 (0.2%)
Hemorrhagic event	1546 (1.3%)	681 (1.0%)	865 (1.7%)	1042 (1.3%)	504 (1.3%)
Intracranial bleed	83 (0.1%)	23 (0.0%)	60 (0.1%)	61 (0.1%)	22 (0.1%)
Upper gastrointestinal bleed	496 (0.4%)	225 (0.3%)	271 (0.5%)	350 (0.4%)	146 (0.4%)
Lower gastrointestinal bleed	122 (0.1%)	50 (0.1%)	72 (0.1%)	86 (0.1%)	36 (0.1%)
Other major bleed	845 (0.7%)	383 (0.6%)	462 (0.9%)	545 (0.7%)	300 (0.7%)
Censoring event					
Maximum follow-up or non-event hospitalization	115298 (95.5%)	67452 (97.4%)	47846 (93.0%)	76981 (95.4%)	38317 (95.6%)

Predicting Events - Cox Model

For exploratory purposes, survival curves for patients who received follow-up in the 7 days post-hospital discharge versus those who did not were estimated using the Kaplan-Meier estimator. Multicollinearity was not found amongst any of the included independent risk factors and aspirin use was not associated with the composite outcome in the univariate Cox regression analysis. Following the backward stepwise approach, the final multivariate Cox model consists of multiple clinical variables as well as the continuity of care variable. The OAC prescribed at discharge, type of OAC user, physician speciality responsible for OAC prescription, discharge disposition, indications for OAC use, anticoagulants dispensed in the 120 days prior to index hospitalization, use of antiplatelets, antibiotics and nonsteroidal anti-inflammatory drugs, both CHA_2DS_2-VASc and HAS-B_ED scores, patients receiving palliative care, previous hospitalizations, other comorbidities including active cancer, dementia, prior thromboembolic events, substance and alcohol abuse, and follow-up with outpatient care between day 0 and day 7 were all variables included in the final model.

Results from the multivariate Cox regression model are reported in Table 3, and significant main effect results are described. Apixaban, rivaroxaban and dabigatran users as compared to warfarin users had a lower risk for the composite outcome at any time between day 8-30 (apixaban HR= 0.82, 95% CI 0.71-0.94; dabigatran HR= 0.73, 95% CI 0.63-0.84; rivaroxaban HR= 0.79, 95% CI 0.71-0.88). Prevalent non-switchers at any time during the study period were 18% less likely to experience the composite outcome than incident users (HR= 0.82, 95% CI 0.69-0.96). Compared to family medicine physicians, patients with either a cardiologist, hematologist or orthopedic surgeon as the physician responsible for the index OAC prescription had a lower risk for the composite outcome at any time during the follow-up (HR= 0.80, 95% CI 0.69-0.93; HR=

0.72, 95% CI 0.52-0.99 and HR= 0.60, 95% CI 0.47-0.77, respectively). Patients who had procedures including joint replacement or major surgery enjoyed a longer event free time (HR= 0.40, 95% CI 0.33-0.50; HR = 0.69, 95% CI 0.60-0.80, respectively). Those with a history of a thromboembolic event also had a 49% lower risk for the composite outcome at any time during the follow-up (HR= 0.51, 95% CI 0.44-0.58).

Antiplatelet or anticoagulant use in the 120 days prior to index hospitalization was associated with increased risk for the composite outcome at any time during the follow-up (HR= 1.18, 95% CI 1.04-1.35; HR= 1.24, 95% CI 1.06-1.45). Similarly, patients who were dispensed an antibiotic in the 30 days prior to index hospitalization were 18% more likely to experience the composite outcome at any time between day 8-30 (HR= 1.18, 95% CI 1.09-1.28). Patients with active cancer (HR= 1.31, 95% CI 1.18-1.45), and patients with a history of substance abuse (HR= 1.53, 95% CI 1.15-2.05) were 31% and 53% more likely to experience the composite outcome, respectively. Patients with a past diagnosis of AF and those who had a deep vein thrombosis or pulmonary embolism during index hospitalization were also associated with increased risk for the composite outcome at any time during the follow-up (HR= 1.12, 05% CI 1.03-1.22 and HR= 2.72, 95% CI 2.43-3.05, respectively). Compared to patients with a CHA_2DS_2-VASc score of 1, patients with a score of 3 or higher were associated with a higher risk for the composite outcome. Patients enrolled in a primary care practise were associated with a 28% increased risk for the outcome during the follow-up (HR= 1.28, 95% CI 1.19-1.37). Palliative patients and those diagnosed with dementia were associated with increased risk for the composite outcome at any time during the follow-up (HR= 2.37, 95% CI 2.16-2.62 and HR= 1.13, 95% CI 1.04-1.23, respectively). Increasing number of hospitalizations in the past one year prior to index hospitalization was associated with a 7% increased risk for the outcome between day 8-30 (HR= 1.07, 95% CI 1.05-

1.20). Patients discharged to a long term or continuing care facility as compared to home were also associated with a 75% increased risk for the outcome between day 8-30 (HR= 1.75, 95% CI 1.60-1.91).

Table 8: Multivariate Analyses of Factors Influencing the Composite Outcome (Time-to-first hospitalization or emergency department visit for a hemorrhage or thromboembolic event, or death from any cause) in the Derivation Cohort.

Predictors	**Composite event**	
	Derivation Cohort (n= 80,650)	
	HR (95% CI)	**p-value**
Index OAC prescribed		
Warfarin	Reference	N/A
Apixaban	0.816 (0.706-0.942)	0.0055***
Dabigatran	0.727 (0.626-0.844)	<0.0001****
Rivaroxaban	0.788 (0.707-0.879)	<0.0001****
Medication use (past 120 d)		
Antiplatelet	1.184 (1.042-1.346)	0.0096***
Nonsteroidal Anti-Inflammatory Drugs*	0.899 (0.791-1.021)	0.0997
Antibiotic use (past 30 d)	1.184 (1.093-1.283)	<0.0001****
Type of OAC user		
Incident	Reference	N/A
Prevalent Non-switcher	0.817 (0.694-0.961)	0.0150**
Prevalent Switcher	0.795 (0.631-1.003)	0.0531
Physician specialty responsible for index OAC prescription		
Family Medicine	Reference	N/A
Cardiologist	0.799 (0.687-0.928)	0.0033***
Hematologist	0.715 (0.516-0.990)	0.0432**
Internal Medicine	0.992 (0.880-1.118)	0.8989
Orthopedic Surgery	0.601 (0.466-0.774)	<0.0001****
Oncology	1.233 (0.727-2.091)	0.4376
Other Surgery	0.852 (0.627-1.157)	0.3042
Other	0.912 (0.834-0.998)	0.0441**
Atrial fibrillation (past 10 yr)	1.122 (1.030-1.221)	0.0081***
Joint replacements (past 35 d)	0.402 (0.326-0.496)	<0.0001****
Major surgery during index hospitalization	0.692 (0.603-0.795)	<0.0001****
Deep vein thrombosis or pulmonary embolism during index hospitalization	2.719 (2.425-3.048)	<0.0001****
Active cancer	1.307 (1.175-1.454)	<0.0001****

Anticoagulant (past 120 d)	1.242 (1.064-1.449)	0.0060***
Comorbidity (past 3 yr)		
Thromboembolic event	0.506 (0.442-0.578)	<0.0001****
Substance Abuse	1.534 (1.149-2.049)	0.0037***
Alcohol Abuse	0.796 (0.609-1.041)	0.0960
CHA_2DS_2-VASc Score		
1	Reference	N/A
2	1.467 (0.879-2.450)	0.1429
3	1.846 (1.121-3.040)	0.0161**
4	2.619 (1.589-4.319)	0.0002***
5	3.028 (1.831-5.010)	<0.0001****
6	3.149 (1.886-5.258)	<0.0001****
7	4.393 (2.589-7.455)	<0.0001****
8	5.494 (3.210-9.403)	<0.0001****
9	5.392 (2.760-10.536)	<0.0001****
HAS-B_ED Score		
1	Reference	N/A
2	0.815 (0.701-0.948)	0.0080***
3	0.951 (0.809-1.118)	0.5452
4	1.100 (0.906-1.334)	0.3370
5+	1.263 (0.854-1.869)	0.2423
Rostered with a primary care practice, physician or team	1.278 (1.187-1.374)	<0.0001****
Palliative patient	2.374 (2.155-2.615)	<0.0001****
Dementia	1.133 (1.045-1.229)	0.0025***
Type of discharge disposition		
Home	Reference	N/A
Long term or continuing care facility	1.747 (1.598-1.910)	<0.0001****
Other	1.300 (0.795-2.128)	0.2961
Continuity of care (7d post-hospitalization)		
Follow-up with outpatient care	0.949 (0.883-1.020)	0.1524
No. of hospitalizations (past 1 yr)	1.074 (1.050-1.099)	<0.0001****

OAC- oral anticoagulant; HR- hazard ratio; CI- confidence interval; CHA2DS2-VASc- Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category; HAS-B_ED- 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.

**p-value ≤ 0.05

***p-value ≤0.01

****p-value <0.0001

Model performance and validation

Model performance in both the derivation and validation cohorts is reported in Table 4. The prediction model had an acceptable discrimination in the derivation cohort (c-statistic= 0.78 for the composite outcome). The overall goodness of fit of the Cox model was poor indicating that the model was not well calibrated ($p < 0.0001$). A split sample analysis of the Cox model yielded a similar c-statistic as the derivation cohort (C statistics = 0.77). Similarly, the overall goodness of fit of the Cox model using the validation cohort was poor indicating that the model was not well calibrated ($p < 0.0001$). Calibration describes how accurately the predictions of the composite outcome from the final Cox regression model reflect the risk for the composite outcome in the observed data [59].

Table 9: Model performance of the final multivariate Cox model for the composite event in the derivation and validation cohorts.

Model Performance	**Derivation Cohort (n= 80,650)**	**Validation Cohort (n= 40,071)**
Goodness-of-fit test statistics, p-value[1]	<0.0001	<0.0001
Discrimination[2]	0.7756	0.7727

1 Goodness of fit algebraically equivalent to Gronnesby and Borgan test
2 Harrell's C-index

3.3 DISCUSSION AND IMPLICATIONS

In this large administrative database study of seniors discharged from a hospital on either warfarin or DOACs, we present a model to predict OAC-related adverse events in the early post-discharge period. We used a Cox regression model to predict the composite outcome of hospitalization or ED visit for a hemorrhage or thromboembolic event, or death. The Cox regression model helps to understand the event-free time of the participants over the observation period more clearly than a logistic regression model [60].

This research adds support to the notion that OAC management post-hospitalization requires a careful assessment of patient and physician characteristics. To our knowledge, this is the first study to examine the association between continuity of care, as measured by outpatient follow-up in the first 7 days post hospitalization, and clinical risk factors and the composite outcome of OAC-related adverse events amongst older users shortly following hospital discharge. Findings from this study are helpful to aid effective management of seniors taking anticoagulants in the high-risk early post-discharge period, however our results are preliminary and should be cautiously interpreted.

The multivariate Cox proportional hazards model used in this research indicates that patients discharged on a DOAC, dispensed the same OAC in the past 12 months, who had a history of a thromboembolic event, have had a recent joint replacement or major surgery had a lower risk for the composite event [61]. Similarly, patients with a cardiologist, hematologist or orthopedic surgeon as compared to a family medicine physician as the physician prescribing the OAC at discharge had a lower risk for the composite outcome at any time during the follow-up. Factors associated with an increased risk for the composite outcome were concomitant antiplatelet or antibiotic use, recent pre-hospital anticoagulant use, and comorbidities including active cancer, atrial fibrillation, deep vein thrombosis or pulmonary embolism during index hospitalization, and dementia [36,62,63]. Patients with a higher CHA_2DS_2-VASc score, with a history of substance abuse, enrolled in a primary care practise, with a high number of previous hospitalizations, receiving palliative care and those discharged into a long term care facility as compared to home were also associated with high risk for the composite outcome.

60.1% of the study cohort received a follow-up visit by outpatient care including primary care physician, medical specialist, nurse practitioner and home care services. Though continuity

of care was a variable in the final multivariate Cox proportional hazards model, it was not a significant predictor for the time to outcome. This was not as hypothesized. It is important to recognize that measuring follow up post hospitalization is a measure of management continuity [64]. Management continuity helps to ensure timely and connected care from different providers [64]. However, it is not an adequate measure of the entire concept of continuity of care including informational and relational continuity [65]. Though previous studies have associated continuity of care with lower health care resource utilization and increased patient satisfaction, those studies measured relational continuity also known as provider continuity [66]. However, literature on early follow-up post hospitalization is not consistent and lacks large, methodologically robust studies measuring its effectiveness on patient important outcomes such as readmissions or ED visits within 30 days of discharge [14,18,67-70]. Randomized controlled trials with interventions targeting the discharge process are complex, targeting multiple aspects of the transition in care out of the hospital, as such inconclusive evidence exists on effectiveness of follow up visits on our outcome of interest in older OAC users [71,72]. Having a follow up may signal worse disease severity but better access to healthcare teams, as such a new measure is needed to measure continuity across organizational boundaries representing all relational, informational and management continuity [20].

Our model performance was acceptable for discrimination but there was poor goodness-of-fit. Calibration describes how accurately the predictions of the composite outcome from the final Cox regression model reflect the risk for the composite outcome in the observed data [59]. A poorly calibrated model is described to under- or over-estimate the risk for the outcome [73]. However, in studies with large sample sizes calibration tests may be misleading as clinically trivial differences between the predicted and observed risks could lead to statistically significant results

[73]. As such, further exploration of the final multivariate Cox regression model is required, including conducting the Gronnesby and Borgan test using STATA.

In our study, an unexpected inverse association between the composite event and history of thromboembolic events was observed. Many risk prediction tools including CHA_2DS_2-VASc associate prior thromboembolic event with a higher risk of stroke [39]. These unexpected relationships require further exploration including conducting a sensitivity analysis with death as a competing risk. This analysis will also separate the fatal and non-fatal OAC-related adverse events as typical in prior literature.

Improving outcomes for seniors discharged on an OAC requires inputs from multiple aspects of the healthcare system, including at the patient, physician and hospital level. Hospitals play an incredibly important role in ensuring informational continuity. In a recent survey, only 16% of Canadian physicians received information needed for follow-up care within 48 hours of their patient's discharge [74]. As such, investments in health information technology that can communicate between hospitals and physician offices could help physician practices identify and monitor care for high-risk patients [75].

Strengths and Limitations

The strengths of our study include the use of a large population of senior patients discharged from the hospital on an OAC, to construct and validate a prediction model for a composite outcome of death, and hospitalization and ED visit for a hemorrhage and thromboembolic event. We minimized selection bias by using all eligible Ontario patients who received provincial health insurance including the coverage of prescription drugs [76,77]. There were rigorous statistical analyses used for model building, performance and validation which helped produce a stable model. Although the model is not well calibrated, the final multivariate

Cox model helps to characterize a more comprehensive list of potential predictors which may be significant in predicting an adverse OAC-related composite event in a population receiving routine clinical care while using OACs in the short-term following hospitalization.

Nevertheless, our study has several limitations. Firstly, we do not have information on true medication adherence only the dispensing of prescribed medications thus the true prevalence of medication use by our cohort may be overestimated. We also do not have information on medications obtained without a prescription, thus the true prevalence of the use of aspirin and NSAIDs by our cohort would be underestimated. This in addition to the poor calibration of the model in both the derivation and validation cohorts weaken the findings based on the data.

As typical of observational research, though many risk factors were explored in association with the composite outcome there may be confounding still present as not all baseline characteristics were measured and therefore could not be adjusted for in the multivariate regression model. As such, caution must be applied when interpreting and comparing the results of this study with other literature.

Finally, our study examined the time to hemorrhage and thromboembolic event resulting in a visit to the hospital, and therefore excludes minor events not resulting in a visit to hospital. Consequently, the number of non-fatal outcomes are underestimated in our study. Furthermore, although the codes used to identify major hemorrhage and thromboembolic events are highly sensitive and specific, care must be taken when comparing our results between studies given the varying definitions of the outcome event.

3.4 CONCLUSION

In this study, we found that continuity of care, as measured by outpatient follow-up in the 7 days post discharge period, was not a significant risk factor associated with the composite

outcome of hospitalization or ED visit for a bleed or thromboembolic event or death in senior OAC users in the short-term following a hospitalization. However, further exploration to improve the current model's calibration and interpretation are required.

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CHAPTER 4: Conclusions, Future Work, Reflections and Tips

4.0 CONCLUSION

This study provides timely predictors of OAC-related adverse events post hospitalization in seniors that may be useful to clinicians, patients and policy-makers in light of newly approved and emerging anticoagulant therapies. In this study, we found that continuity of care, as measured by outpatient follow-up in the 7 days post discharge period, was not a significant risk factor associated with the composite outcome of hospitalization or Emergency Department (ED) visit for a bleed or thromboembolic event or death in senior OAC users in the short-term following a hospitalization. However, further exploration to improve the current model's calibration and interpretation are required.

4.1 FUTURE WORK

The current research work only addresses the primary objective of the proposed protocol. However, ongoing work is required to complete the results, and plan future analyses.

This would include exploring the violation of the proportional hazards' assumption for the continuity of care and discharge disposition variables. This could be accomplished by creating strata for the different levels of each variable; however, this would result in loss of information as the hazard for the strata variable would no longer be calculated in the multivariate Cox proportional hazards model [1]. Furthermore, the present model is poorly calibrated as such an exploration of outliers and highly influential observations is required [1].

Currently, only the main effects of all risk factors were explored in this analysis. However, it is important to note that interactions, which occur when the effect of one independent variable may depend on the level of another independent variable, were not explored [2]. Interaction between OAC type and potentially interacting drugs including antibiotics, and antiplatelets

amongst others should be explored, if deemed clinically important. Lastly, sensitivity analyses including the competing risk analysis and one with myocardial infarction in the outcome definition are still pending. These will be explored for the final manuscript publication.

4.2 REFLECTION AND TIPS FOR SIMILAR FUTURE RESEARCH

Working with large administrative health data posited multiple challenges and learnings. The following is a list of suggestions for future researchers who are not already experienced with working with the linked Ontario health administrative data held within ICES:

1. Obtaining access to data is a long process (~6-12 months), therefore start early with developing your protocol and data creation plan and understanding which databases you will need access to for your analysis. This may include finding validated combination of codes to define certain comorbidities and risk factors.
2. Getting access to ICES data can be costly so having a clear data creation plan and a budget is important. Ideally, you can get all of the variables coded in a format ready for analysis by the ICES analysts but if budget is tight you can choose to obtain all of the datasets and then code for the comorbidities and variables of interest.
3. Check the quality of your data by looking for missing data and make sure that all requested data are in the format you requested.
4. If you are manipulating the data to create variables using multiple sources, ex. hospitalization records and physician billings, it is important to understand the organization of each database as coding in each may be different.
5. If you have remote access to the data, you may not have access to ICES-developed macros, therefore, it is important to learn more advanced codes such as the DO Loop in SAS.

6. If you are proficient in another statistical software, including R or STATA, please be aware that ICES analysts code in SAS so getting technical help from them may not be feasible.
7. Verify that your code is working as intended by running descriptive statistics. Consult ICES analysts and your team's statisticians to verify what you are seeing is expected or logical.
8. Consulting ICES staff is very helpful; however, they do have limited time, so detailed emails are the most time and cost-efficient method of communicating with them.
9. While coding your analysis in SAS via the remote access environment through ICES, efficient coding is very important to avoid lack of memory errors. If an ICES guidebook on your analysis has been developed for ICES analysts, obtain access to it. This will help troubleshoot lack of memory issues in SAS.

Overall, working with large administrative data requires attention to detail but is a process of trial and error. Start early and reach out to multiple colleagues for help!

4.3 REFERENCES

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