


BMJ Open Predictors of oral anticoagulant-associated adverse events in seniors transitioning from hospital to home: a retrospective cohort study protocol

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To cite: Benipal H, Holbrook A, Paterson JM, *et al*. Predictors of oral anticoagulant-associated adverse events in seniors transitioning from hospital to home: a retrospective cohort study protocol. *BMJ Open* 2020;**10**:e036537. doi:10.1136/bmjopen-2019-036537

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-036537>).

Received 18 December 2019
Revised 01 May 2020
Accepted 28 May 2020

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 among 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 OAC from September 2010 to March 2015 in Ontario, Canada. The primary outcome is a composite of the first hospitalisation or emergency department visit for a haemorrhage 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 authorised 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 randomised trials.

Trial registration number ClinicalTrials.gov Identifier: NCT02777047; Pre-results.

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.^{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

Strengths and limitations of this study

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

harm, primarily bleeding and thromboembolic events.^{4,5}

It is estimated that between 2013 and 2014, OACs were implicated in 28% (95% CI 23% to 32%) and 39% (95% CI 33.7% to 43.8%) of emergency department (ED) visits in the USA for adverse drug events among adults aged 65–79 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 hospitalisations among seniors between 2006 and 2011.⁷

Observational studies using population-level data report even higher adverse event rates for OAC users during periods of transitions in care, specifically during the early post-hospitalisation period. Among the elderly, a bleeding risk of 26.4% (95% CI 25.3–27.4) per person-year and a thromboembolic event risk of 32.4% (95% CI 31.3 to 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 WHO as ‘the degree to which discrete



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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 hospitalisations 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 postdischarge as best practice to improve continuity of care.^{10 19–24}

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

This study aims to identify important risk factors, both clinical and continuity of care, which predict OAC-related harm in the short-term period following hospitalisation. 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-hospitalisation or an ED visit for a haemorrhage 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 hospitalisation.

METHODS AND ANALYSIS

Reporting will be compliant with Strengthening the Reporting of Observational Studies in Epidemiology 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 minimise

selection bias as the database includes the entire population of interest.^{29 30}

Setting

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

Data sources

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

Observation period

We define the study's index date as the date of OAC dispensing, which had to be within 1 day of hospital discharge. The patient accrual period will be 1 September 2010–31 March 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.³⁷

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 hospitalisation or an ED visit for a thromboembolic or haemorrhagic event within the 7-day blanking period will be excluded. For those who remain in the cohort, healthcare 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-hospitalisation (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 hospitalisation 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.^{38 39}

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 1 day of discharge. Patients with a most responsible discharge diagnosis of major bleeding, defined as any bleeding event that was the cause for the hospitalisation or contributed to the greatest fraction of the length of stay, will be excluded.⁴⁰ We will use the Ontario Health Insurance Plan Registered Persons Database, which contains insurance coverage, demographic, place of residence and vital status information, together with the Canadian Institute

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 hospitalisations.
Canadian Institute for Health Information–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 enrolment 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 Database (CHF) ⁵⁴ ; Ontario Dementia Database (DEMENTIA) ⁵⁵ ; Ontario Diabetes Database (ODD) ⁵⁶ ; and Ontario Hypertension Dataset (HYPER). ^{57 58}
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 utilisation 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 health 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 healthcare 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 assess 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.

for Health Information Discharge Abstract Database, to identify the study patients. We will also access the prescription drug claims history of eligible patients via the Ontario Drug Benefit Plan Database. These datasets are linked using unique coded identifiers and will be analysed at ICES (www.ices.on.ca).

The age threshold of 66 years will be applied to capture prescription use by study participants at least 1 year prior to study enrolment, as Ontario Drug Benefits programme eligibility begins at the age of 65 years. This will avoid

incomplete or missing prescription drug data for study participants.⁴¹

Variables

Outcomes

The primary outcome will be a composite of hospitalisation or ED visit for a haemorrhage or thromboembolic event, or death from any cause. These events are standard in pivotal trials and are the main OAC-associated serious

Table 2 Diagnosis and procedure codes used to define thromboembolic outcomes

Thromboembolic event type	ICD-10 codes	Canadian Classification of Health 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	
Ischaemic 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 ischaemic 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	

ICD-10, International Classification of Diseases, 10th revision.

adverse events. Including death also avoids the problem of competing risks.^{42–46}

Thromboembolic events will include venous thromboembolic events (deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (ischaemic stroke or transient ischaemic 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.^{47–51} Haemorrhagic events will include intracranial bleeds, upper and lower gastrointestinal bleeds and any other bleed that required a hospital admission or a visit to an ED. [Table 3](#) lists the ICD-10 diagnosis codes used to define haemorrhage. Validation studies found equivalent ICD-9 diagnosis codes to have 94% sensitivity and 83% specificity for major haemorrhagic events.⁴⁹

The outcomes will be ascertained using Canadian Institute for Health Information Discharge Abstract Database, Canadian Institute for Health Information National Ambulatory Care Reporting System, and Ontario Health Insurance Plan Registered Persons Database.^{52 53}

Risk factors

[Table 4](#) summarises 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 neighbourhood 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.⁵⁴

Characteristics of the index hospitalisation including type of hospital, length of index hospitalisation and

Table 3 Diagnosis codes used to define haemorrhage outcomes

Haemorrhage type	ICD-10 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

ICD-10, International Classification of Diseases, 10th revision.

Table 4 Clinical and continuity of care variables and data sources

Variable	Data source
Patient characteristics	
Age	RPDB
Sex	
Income quintile	Statistics Canada
Rural residence	Census Postal Code Conversion File
Rostering: patient enrolled in a primary care organisation, team or with a primary care physician	CAPE
Palliative patient: look-back window of 6 months	OHIP, CIHI-DAD, CIHI-NACRS, RAI-CA, RAI-HC, HCD, CCRS
Characteristics of index hospitalisation	
Type of hospital: teaching, community, small	Ontario Ministry of Health and Long-Term Care
Length of index hospitalisation	CIHI-DAD
Specialty of the physician responsible for index OAC prescription: general/family practitioner; cardiology; haematology; internal medicine; orthopaedic 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 CHA ₂ DS ₂ -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	HYPERS
Diabetes mellitus	ODD
Prior stroke/transient ischaemic stroke	CIHI-DAD
Peripheral vascular disease	

Continued

Table 4 Continued

Variable	Data source
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 hospitalisations in the past year	CIHI-DAD
Recent anticoagulant use (120 days)	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 that potentially interact with OACs	
Continuity of care – healthcare contact within 7 days of discharge from index hospitalisation	

Continued

**Table 4** Continued

Variable	Data source
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

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

CAPE, Client Agency Program Enrollment Database; CCRS, Ontario Continuing Care Reporting System; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke, vascular disease, age 65–74 years, sex category; CHF, Ontario Congestive Heart Failure Database; CIHI-DAD, Canadian Institute for Health Information–Discharge Abstract Database; CIHI-NACRS, Canadian Institute for Health Information–National Ambulatory Care Reporting System; DEMENTIA, Ontario Dementia Database; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio (excluded), elderly (>65 years), drugs/alcohol concomitantly; HCD, Ontario Home Care Database; HYPERT, Ontario Hypertension Dataset; IPDB, ICES Physician Database; OCR, Ontario Cancer Registry; ODB, Ontario Drug Benefit Programme Database; ODD, Ontario Diabetes Database; OHIP, Ontario Health Insurance Plan Claims History Database; OMHRS, Ontario Mental Health Reporting System Database; RAI-CA, Resident Assessment Instrument—Contact Assessment; RAI-HC, Resident Assessment Instrument—Home Care; RPDB, Ontario Health Insurance Plan Registered Persons Database.

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 categorised into three categories of OAC users including incident, prevalent non-switchers and prevalent switchers.

Existing comorbidities may be associated with outcomes^{55–57}; therefore, comorbidities including dementia and diabetes will be captured.^{33 34} In addition, patients with a history of substance or alcohol abuse in the past 3 years prior to cohort entry will be identified.⁵⁸ 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. Hospitalisation or ED visits in the 3 years prior to cohort entry for thromboembolic or haemorrhagic events will also be recorded.

Several indices, including the Deyo-Charlson Comorbidity Index, a general comorbidity measure developed to predict mortality, will also be calculated to describe the cohort.⁵⁹ Validated clinical scores used to guide anticoagulation of patients including the congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke, vascular disease, age 65–74 years, sex category (CHA₂DS₂-VASc) risk stratification scheme for predicting thromboembolism in patients with AF will be

calculated.⁶⁰ Additionally, the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly (>65 years), drugs/alcohol concomitantly (HAS-BLED) score, which was developed to support clinical decision making regarding anticoagulant therapy in AF patients by predicting bleeding risk in these patients, will be calculated.⁶¹ Since data on labile international normalised ratio are 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 min or longer (excluding same day surgery) during index hospitalisation, presence of a mechanical heart valve and deep vein thrombosis or pulmonary embolism during index hospitalisation.^{62–64} These indications will be inferred from corresponding diagnosis and procedure information, as indications for prescriptions are not recorded in Ontario prescription drug claims.

We will be adjusting for the presence of drug therapies hypothesised to influence the risk of our outcome through potential interactions with OACs by including use of prescription non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, amiodarone, prescription aspirin and antiplatelets use in the 120 days prior to cohort entry and antibiotic use in the 30 days prior to cohort entry.^{64–66} Recent pre-hospital anticoagulant use was also captured.

Continuity of care will be operationalised 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 that may help reduce hospital readmissions.^{67 68} In addition, we will capture whether patients had a follow-up visit within 1 week post-discharge with any physician with whom they had had at least two visits in the 12 months preceding the index hospitalisation (community physician) or at least one 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-hospitalisation may have a beneficial impact on follow-up rates and reduce risk of death or re-admissions.⁶⁹

Quality checks, missing data and extreme values

Data are unlikely to be missing at random.^{41 52 70} 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.^{67 71 72} DOAC users tend to be younger with fewer comorbidities than warfarin

users.⁷³ To control for confounding, we will include variables such as age, sex, presence of specific comorbidities, concomitant medications, remote residence, neighbourhood income quintile and physician specialty among other independent variables in the model as potential risk factors. Furthermore, the inclusion criteria for study participants may exclude prevalent OAC users who have an existing supply of OACs. This biases the study cohort to include more patients who start OAC therapy post-hospitalisation. However, the current participant inclusion criteria allow us to study the impact of the index hospitalisation on outcomes for OAC users.

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

Sample size

For Cox regression, a fitted model is likely to be reliable and stable when the number of participants with the outcome (ie, either first hospitalisation or ED visit during follow-up for a haemorrhage or arterial or venous thromboembolic event, or death) is 20 times the number of covariates.⁷⁵ We anticipate that up to 30 covariates will be included in the Cox regression model; therefore, a minimum of 600 patients with at least one of the outcomes that form the composite will be required to devise the models in this cohort. This is feasible as a similar study reported haemorrhage and thromboembolic event rates of about 26 and 34 per 100 person-years in the first 30-day 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 summarised using frequency and percentage. Continuous variables will be summarised using mean and SD or median and IQR, when results are skewed. Person-time of follow-up will also be captured.

A summary of all planned analysis is provided in [table 5](#). Given that the primary outcome is a time-to-event outcome, Cox proportional hazards model will be used to determine the association between the composite outcome and all risk factors including patient demographic, index hospitalisation descriptors, comorbidity, drug indications, potential drug interactions and continuity of care variables within 1 month of hospital discharge.

Model construction

Model derivation and validation will be based on a split-sample method.⁷⁶ Two-thirds of the study participants will be randomly assigned to a model derivation cohort, and one-third will be reserved as an independent validation

cohort.⁷⁷ Both cohorts will be compared with respect to clinical and continuity of care variables.

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

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

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

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

Sensitivity analysis

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

Moreover, a competing risk analysis is planned where all-cause mortality will be treated as a competing risk for haemorrhagic and thromboembolic events. A

Table 5 Statistical plan summary

Objective/analyses	Outcome	Type	Method of analysis	Independent variables
Primary objective	Definition			
To determine which clinical and continuity of care variables predict the outcome in senior OAC users post-hospitalisation.	Re-hospitalisation or ED visit for a haemorrhagic or thromboembolic event or mortality in 30 days.	Time to event.	Cox proportional hazards model.	Demographic <ul style="list-style-type: none"> ▶ Income quintile. ▶ Rural residence. ▶ Patients enrolled under a primary care physician or organisation. ▶ Palliative patient.
Sensitivity analyses				Index hospitalisation characteristics
Include myocardial infarction in the definition of thromboembolic event outcome.	Re-hospitalisation or ED visit for a haemorrhagic or thromboembolic event or mortality in 30 days.	Time to event.	Cox proportional hazards model.	<ul style="list-style-type: none"> ▶ Type of hospital. ▶ Specialty of OAC prescribing physician.
Competing risk analysis.	Re-hospitalisation or ED visit for a haemorrhagic or thromboembolic event in 30 days.	Time to event.	Cause-specific Cox proportional hazards model.	<ul style="list-style-type: none"> ▶ Type of OAC dispensed. ▶ Type of discharge. ▶ Type of OAC user. ▶ Incident. ▶ Prevalent non-switcher. ▶ Prevalent switcher
Validation				Comorbidities
Internal validation of the primary model.	Re-hospitalisation or ED visit for a haemorrhagic or thromboembolic event or mortality in 30 days.	Time to event.	Split-sample method.	<ul style="list-style-type: none"> ▶ CHA₂DS₂-VASc. ▶ HAS-BLED. ▶ Dementia. ▶ Delirium. ▶ Obesity. ▶ Underweight. ▶ Antiphospholipid syndrome. ▶ Active cancer. ▶ Prior thromboembolic or haemorrhagic event. ▶ Substance abuse. ▶ Alcohol abuse. ▶ Hospitalisation in past year. ▶ Recent anticoagulant use.
				Indications
				<ul style="list-style-type: none"> ▶ Atrial fibrillation. ▶ Joint replacement. ▶ Major surgery. ▶ Mechanical heart valve. ▶ Deep vein thrombosis or pulmonary embolism.
				Potential drug interactions
				<ul style="list-style-type: none"> ▶ NSAIDs.* ▶ SSRIs. ▶ Amiodarone. ▶ Aspirin.* ▶ Antiplatelets. ▶ Antibiotics. ▶ Number of drugs, potentially drugs interacting with OACs, dispensed.
				Continuity of care
				<ul style="list-style-type: none"> ▶ Follow-up with primary care physician, nurse practitioner, medical specialist or home care services within 7 days of discharge from index hospitalisation.

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

CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65–74 years, sex category; ED, emergency department; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio (excluded), elderly (>65 years), drugs/alcohol concomitantly; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulant; SSRIs, selective serotonin reuptake inhibitors.

cause-specific Cox proportional hazards model will be constructed.⁸³ Predictors and their coefficients in the cause-specific hazard models will be compared with those in the full Cox model.

Model validation

Once the final model is developed, it will be assessed in the separate validation cohort of patients. The predictive accuracy of the model will be assessed using tests

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

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

Patient and public involvement

The publicly funded research programme 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 OAC management provided suggestions for predictors. Patients did not contribute to the actual writing or editing of this document.

ETHICS AND DISSEMINATION

All study data reside and are analysed at ICES (www.ices.on.ca). ICES is a prescribed entity under Section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorises 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 randomised trials.

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Collaborators None Declared.

Contributors 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. All authors approve the attached manuscript for publication and take accountability for all aspects of the work.

Funding This work is supported by a grant from the Canadian Institutes for Health Research – grant # 365 834 and the Hamilton Academic Health Sciences Organization – grant # HAH-16-06 awarded to AH. This study was also supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Parts of this material are based on information compiled and provided by the MOHLTC, Cancer Care Ontario and the Canadian Institute for Health Information. We would like to thank IMS Brogan Inc for use of their Drug Information Database.

Disclaimer The conclusions, opinions and statements expressed herein are those of the authors and do not necessarily reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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