Oral Anticoagulant-associated Adverse Event Rates are High in the Post-Hospital Discharge Period

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Funding Statement
This study was funded by grants to Dr Holbrook from the Hamilton Academic Health Sciences Organization AFP innovation fund (#HAH-16-06) and from the Canadian Institutes for Health Research (#365834), and by the Ontario Drug Policy Research Network (ODPRN), which is funded by grants from the Ontario Ministry of Health (MOH).

Declaration of Authors Competing Interests
Anne Holbrook has served as an expert policy advisor for national, provincial and local hospital public drug plans for several decades. All other authors report no relevant competing interests.

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Abstract

Background

Oral anticoagulants (OACs) are commonly used and are a top medication safety priority. Transitions in care, particularly for older adults taking multiple medications, have been recognized as patient safety risks. Our objective was to measure the rates of hemorrhage and thromboembolic events amongst senior OAC users early post-hospital discharge compared to later.

Methods

This was a population-based retrospective cohort study among Ontario residents, aged 66 years and older, who started, continued or resumed OAC therapy after hospital discharge between 2010 and 2015. Patient-level administrative healthcare data were linked, including prescription drug claims, vital status, demographics, and hospitalizations. We calculated the hemorrhage and thromboembolic rates over a one-year follow-up period, stratified by the first 30 days post-discharge and the remainder of the year. We examined the influence of patient sex, prevalent versus incident use, or switching OAC on the event rate.

Results

123,139 patients were included in the study, median age 78 years, 55.6% female, 26.4% with Charlson comorbidity score > 2. The rate of hemorrhage was highest during the first 30-days post discharge at 25.8 per 100 person-years (95% CI 24.8-26.8), falling to 15.7% (95% CI 15.3-16.1) during the remainder of the year. The risk of thromboembolic events per 100 person-years was 19.3 (95% CI 18.4-20.2) during the first 30-days post-discharge versus 6.9 (95% CI 6.6 – 7.1) during the remaining 11 months. Males had higher rates of events than females.

Interpretation

The first month following hospital discharge identifies a very high-risk period for OAC-related adverse events amongst older adults.

Word count (abstract): 256
Word count (body): 2496

Introduction

Background

Oral anticoagulants (OACs), including warfarin and the direct-acting oral anticoagulants (DOACs), are highly effective for the prevention of stroke and systemic embolism in patients with atrial fibrillation, as well as for the treatment and prevention of venous thromboembolism (VTE).[1-5] More than 7 million prescriptions in Canada and more than 37 million prescriptions in the United States are filled annually for OACs.[6, 7] Despite their benefit, oral anticoagulants (OACs) are considered high alert medications because of their risk of significant harm - mainly bleeding, or thromboembolic events and death if they are not well managed.[8] We and others have found that OACs are the most common drug-related cause of emergency department visits or hospitalizations amongst older adults, with accompanying high mortality rates.[9-11]

The immediate post-hospitalization period can be high risk for adverse events as the transition to home is a complex process involving multiple providers, locations, testing, medication changes with imperfect reconciliation, at a time when patients are still recovering. Approximately one fifth of Medicare patients discharged from hospital require a re-hospitalization within 30 days.[12] Studies on the rates of medication-related adverse events in the early post-hospitalization period suggest these are high.[13, 14] Our previous study demonstrated a four-fold greater bleeding risk in Ontario seniors on warfarin in the first 30 days after hospital discharge compared to the remainder of the 5-year follow-up.[15] Very little is known about the high-risk periods for bleeding or thromboembolic events in the era of DOAC use.

Objectives

We aimed to measure thromboembolic and bleeding event rates associated with OAC use in the early post-hospital discharge period (within 30 days) compared to the remainder of the year, hypothesizing that the early post-discharge period would be higher risk for adverse events compared to later.

Methods

Study Design and Setting

A retrospective, population-based cohort study was conducted in Ontario, Canada. All residents have access to publicly funded physician and hospital care, and seniors also have access to prescription medications with a low or no co-pay. Study methods and reporting follow STROBE and RECORD-PE recommendations.[16, 17] A detailed protocol with a pre-specified analysis plan was prepared and registered at ICES prior to accessing data.

Ethics

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.

Data Sources

Multiple administrative health datasets were linked for this study, using unique, encoded identifiers. Details of the databases and their contents is provided in Table 1.[18] In brief, the Ontario Health Insurance Plan (OHIP) database contains billing and diagnostic codes for physician services, the Ontario Drug Benefit (ODB) database contains details of outpatient prescription drugs dispensed to seniors, and the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and National Ambulatory Care Reporting System (CIHI-NACRS) detail diagnoses and procedures provided during hospital admissions and emergency department (ED) visits, respectively. Demographics and vital status were obtained from the OHIP Registered Persons Database. Disease-based registries were used for cancer, diabetes, congestive heart failure, and hypertension.[19-22] Physician specialities were identified from the ICES Physician Database. There is a large published experience on the validity and completeness of these population-based databases for drug-related adverse events requiring hospitalization or ED visits.[23] In this study, all diagnoses were coded in ICD-9 or ICD-10, procedures used the Canadian Classification of Interventions codes, and medications were identified through Health Canada Drug Identification Numbers. A list of codes used in the study is available upon request.

Participants

Eligible patients were 66 years of age or older who started, continued or resumed OAC therapy after hospital discharge between September 2010 and March 2015. OACs included warfarin, dabigatran, rivaroxaban, and apixaban. Patients who had been admitted for a major bleed were excluded, as OAC therapy would be contraindicated in many cases. Patients were also excluded if they received more than one type of OAC at cohort entry or did not have provincial health coverage. Patients during their first year of eligibility for prescription drug coverage at 65 years were excluded to avoid incomplete medication records. Figure 1 shows the details on cohort selection.

OAC Exposure

We defined cohort entry as the dispensing date of the first post-discharge outpatient OAC prescription in the ODB database within one day of discharge. This was captured on the day prior to, day of, or day after the hospital discharge date. Ongoing use of OAC therapy was defined by successive refills of any OAC prescription within 30 days or 1.5 times the days' supply of the most recent prescription, whichever was greater. This period allowed for periodic adjustments to doses, short pauses, and variable timing of refills. If this timeframe for refills was exceeded, patients were deemed to have discontinued treatment and were followed for 30 days or 1.5 times the days' supply of their final prescription, whichever was longer.

We stratified eligible patients into incident and prevalent OAC users. Incident users were individuals who had not previously been dispensed an OAC in the one year prior to cohort entry, whereas prevalent users were individuals who had been dispensed an OAC in that time. Prevalent users were further divided into two groups: switchers and non-switchers. Non-switchers continued the same OAC after discharge as they had been taking before hospitalization, while switchers changed to a different OAC prescription after hospital discharge.

Outcomes

Our primary outcomes were thromboembolic and hemorrhagic events requiring admission to hospital or visit to the emergency department. Thromboembolic events included venous events -

deep vein thrombosis or pulmonary embolism, and arterial events - ischemic stroke or transient ischemic attack, peripheral vascular disease embolism, and systemic embolism. Hemorrhages were categorized as intracranial, upper or lower gastrointestinal, or other major bleeds. Multiple studies have established the validity of administrative data for thromboembolic events and hemorrhages.[24-30]

Patients were followed until one of the following events occurred: death, OAC therapy discontinuation, hospitalization for more than 5 days for reasons other than hemorrhage or thromboembolic event, 365 days of follow-up, or the end of the study period (March 31, 2016). If a patient had multiple admissions for any outcome of interest during follow-up, each event was included in calculating the rate of events. Major hemorrhagic and thromboembolic events during the post-discharge period were assessed at intervals of 0 to 30 days, 31 to 364 days, and 0 to 364 days.

Figure 2 shows the cohort timeline and definitions.

Variables

Baseline demographics included age, sex, and rural residence (based on postal codes). Data regarding the patients' care included the OAC dispensed at index prescription date, and physician specialty on the index prescription. One or more indication for each patient's OAC included: a) atrial fibrillation (ED visit or hospitalization for atrial fibrillation within the past 10 years), b) prevention of VTE (hip or knee joint replacement in the 35 days prior to cohort entry, or major surgery during index hospitalization), c) treatment of VTE (diagnosis of acute deep vein thrombosis or pulmonary embolism during the index hospitalization) or d) active cancer (codes for cancer-related surgery, chemotherapy or radiation in the Ontario Cancer Registry, DAD, or OHIP in the 180 days prior to cohort entry).

Other past medical history collected at baseline included thromboembolic and hemorrhagic events within the previous 3 years, hospitalizations in the past year, recent medications that could adversely interact with OACs, and comorbidity burden using the Deyo-Charlson Comorbidity Index.[31] Individual risks of stroke using CHADS-VASc score and risks of major bleeding using HAS-BED score (HAS-BLED without INR data), were calculated using previously validated database registries.[19, 32-35]

Statistical Analysis

We compared baseline characteristics between incident and prevalent users of OACs, and within the prevalent users, those who switched their OAC at the index prescription compared to pre-hospital period and those who did not switch.

Crude rates for hemorrhagic and thromboembolic events were calculated during the first 30 days, 31-364 days, and the entire year after initiating OAC therapy. Intention-to-treat principles were used for the analysis. The rate was calculated as the total number of events leading to the hospitalization or an emergency department visit for a hemorrhagic or thromboembolic event divided by the person-years available during the interval. The analysis was stratified to the type of OAC therapy user (incident, switcher or non-switcher).

Results

Participants

Data for 3,036,285 patients who were discharged from an Ontario hospital during the accrual period, were assessed for eligibility. Once exclusions were made for missing identifiers, younger age, no OAC prescription within one day of hospitalization, death prior to cohort entry, and duplicate prescription for OAC, a total of 123,139 eligible patients were identified. Figure 1 details the flow chart for exclusions.

Table 2 shows the baseline characteristics of the cohort and strata.[36] The mean age of participants was 78 years (standardized difference [SD], 7.73), with 55.6% females, and 16.2% residing in a rural area. Indications for the OAC included atrial fibrillation (51.1%), recent joint replacement (36.0%), major surgery during index hospitalization (17.9%), active cancer (6.4%), and DVT or PE diagnosed during index hospitalization (5.2%). Patients were most often dispensed warfarin (48.1%) or rivaroxaban (41.7%), compared to dabigatran (5.4%) and apixaban (4.8%). Overall, 70,140 (57.0%) patients were incident users and 52,999 (43.0%) were prevalent users. Prevalent users tended to be older (mean age of 81.1 ± 7.6 versus 76.1 ± 7.1) and received their index prescriptions from family physicians more often than incident users (54.6% versus 18.0%).
Of the 52,999 prevalent users, 49,325 were non-switchers (93.1%) and 3,674 were switchers (6.9%). Of these, switches from DOAC to warfarin occurred in 40.3% of switchers and warfarin to DOAC in 59.7% of switchers. There were 9784 deaths over the year of follow-up, representing 7.9% of the cohort.

Main Results

Rates of major hemorrhage (Table 3a and Figure 3) declined from 25.8 per 100 person-years (PY) (95% CI 24.8-26.8) in the first 30 days post-discharge to 15.7 per 100 person-years (95% CI 15.3-16.1) over the remaining 11 months. Prevalent users, with similar rates for switchers and non-switchers, experienced a higher overall rate of hemorrhage at 20.4 per 100 PY (95% CI 19.9-20.9) compared to incident users at 14.6 per 100PY (95% CI 14.1-15.1). In addition, males were more likely to experience a hemorrhage compared to females at 21.3 (95% CI 20.8-22.0) versus 14.8 (95% 14.4-15.3) PY respectively, over the year. Upper gastrointestinal bleeds were the most common type of specified bleed with an annual rate at 4.8 per 100 PY (95% CI 4.6-5.0).

Thromboembolic events, (Table 3b and Figure 4) occurred at a rate of rate was 19.3 per 100 PY (95% CI 18.4-20.2) in the first 30 days, decreasing to 6.9 per 100 PY (95% CI 6.6-7.1) over the remainder of the year. A total of 2485 of 4643 (53.5%) events over the year were arterial, including 1696 (36.5%) ischemic strokes/TIA or systemic embolisms, compared to 1180 (25.4%) DVT and 978 (21.1%) PE, representing venous events. The rate of thromboembolic events for incident users at 10.0 per 100 PY (95% CI 9.6-10.4) was higher than for prevalent users at 8.9 per 100 PY (95% CI 8.5-9.2). In contrast to patients with hemorrhagic events, patients with thromboembolic events were much more likely to have just switched their OAC, at 91.3% of prevalent users. Males had a higher rate of thromboembolic events compared to females at 10.0 per 100 (95% 9.6-10.5) versus 8.9 per 100 PY (95% CI 8.5-9.2) respectively.

Interpretation

Key Results

This study is unique in its focus on oral anticoagulant-related adverse events early versus later following hospital discharge. Assuming a medication-focused approach to outcomes as opposed to a disease-specific approach, provides a broader view of medication safety. In this case, both major hemorrhages and thromboembolic events were defined to be highly clinically relevant in that hospitalization or ED visit was required. In this population-based cohort study involving older Ontarians, hemorrhages and thromboembolic event rates were very high in the first 30 days after hospital discharge, considerably higher than the remainder of the year. Although incident users included a large number of short-term users (e.g., VTE prophylaxis after orthopedic surgery), their 30-day event rates were still high, at 21.4 per 100 PY (95% CI 20.2-22.6) for thromboembolic events and 21.9 per 100 PY (95% CI 20.6-23.1) for hemorrhagic events. Prevalent users of OACs were more likely than incident users to experience a hemorrhagic event at any time point, but less likely to suffer a thromboembolic event. Event rates at every point except later thromboembolic events, were significantly higher in males than females. Switching between OAC agents was not found to elevate the risk of adverse events. The mortality rate in our cohort was also relatively high at 7.9% during the year of follow-up.

The main results are in line with observational studies reporting a high prevalence of OAC-related adverse drug events leading to emergency room visits and hospitalization of patients, and support the contention that transitions in care for patients should be a target for research on interventions intended to lower adverse outcomes.[37, 38] A recent systematic review reported that frequent patient contact, dedicated teams for discharge planning and home visits were found to be most effective at reducing early readmissions.[39] In the Canadian context, a large cohort study found that 30-day non-elective readmissions and deaths could be reduced with physician follow-up, particularly by the physician involved in the patient's hospital care.[40] Randomized trials of targeted strategies to reduce readmission in patients discharged with OACs are still needed and are high-priority.

Sex differences in the rates of venous thromboembolic events have been previously reported, although the reasons for higher rates in males are not entirely clear.(41-45) Stroke rates in patients with atrial fibrillation may not vary by sex.(46) Bleeding rates for men on oral anticoagulants, either DOACs or warfarin, have also been reported to be higher than in women(45, 47) but refuted by others, so sex differences in hemorrhage rates on OACs are also unclear.

Limitations

Our study has several strengths, including large sample size, validated data sources, and inclusion of virtually all seniors in a large, diverse province of Canada.[48] However, there are limitations. First, the results cannot be generalized to younger groups of people. Second, minor events which do not lead to hospitalization or ED visits can still be morbid and adversely affect quality of life, but are not captured in these data. Third, these observational data which are collected as part of routine clinical care are always at some risk of information bias. However, missing data was very rare at less than 0.07% and misclassification bias for key elements including hospital discharge, prescription dispensing, and morbid outcomes requiring hospitalization or ED visit, is known to

be low.(49-51) A follow-up study on predictors of the outcome events, will address unmeasured confounding and death as a competing risk of outcomes, in more detail.

Conclusion

This study shows that post-hospital discharge adverse events related to OACs are common amongst older adults in Ontario, and are very common in the first 30 days post-discharge. This supports the need for trials of organized discharge and early post-discharge interventions as well as further analyses of predictors of adverse events.

Funding

This study was funded by grants to Dr Holbrook from the Hamilton Academic Health Sciences Organization AFP innovation fund (#HAH-16-06) and from the Canadian Institutes for Health Research (#365834), and by the Ontario Drug Policy Research Network (ODPRN), which is funded by grants from the Ontario Ministry of Health (MOH).

Acknowledgements

This study was supported by ICES, which is funded by an annual grant from the Ontario MOH. Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health, the Canadian Institute for Health Information, Cancer Care Ontario, and Brogan Canada Inc. The analyses, conclusions, opinions and statements expressed herein are those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Accessibility of protocol, raw data, and programming code

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

This study included several ICES scientist investigators and analysts who have full access to both the underlying source data files and the final analytic data set. Standard data cleaning methods were used.

Table 1: Description of ICES Databases[18]

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 Emergency Department visits
The DrugList File	List of Drug Identification Numbers used in Canada from 1990 forward. Contains drug and product names, manufacturer, subclass information, pharmacy classification group codes, drug strength, route of administration, and first and last dispensing dates of drugs.
ICES-Derived Cohorts	Validated cohorts of individuals with specific diseases and conditions, including the Ontario Congestive Heart Failure (CHF) Database; Ontario Diabetes Database (ODD); Ontario Hypertension Dataset (HYPER)
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 Drug Benefit (ODB)Program Database	Records of dispensed outpatient prescriptions paid for by the provincial government
Ontario Health Insurance Plan(OHIP) Claims History Database	Claims for physician services paid for by the provincial government
Ontario Health Insurance Plan (OHIP) Registered Persons Database (RPDB)	Demographic, place of residence and vital status information for all persons eligible to receive insured heath services in the province
Statistics Canada Census Postal Code Conversion File	Information on rural residence and income quintiles of residents

Table 2: Baseline Characteristics*

	Entire cohort				Prevalent users		
	Entire cohort n = 123,139	Incident OAC Users n = 70,140	Prevalent OAC Users n = 52,999	SD§	Prevalent Switcher n = 3674	Prevalent Non-switcher n = 49,325	SD§
Demographics							
Age†	78.2 (7.7)	76.1 (7.1)	81.1 (7.6)	0.69	79.4 (7.3)	81.23 (7.6)	0.24
Age 66-74 years	44,343 (36.0)	32,603 (46.5)	11,740 (22.2)	0.53	1,024 (27.9)	10,716 (21.7)	0.14
Age >75 years	78,796 (64.0)	37,537 (53.5)	41,259 (77.8)	0.53	2,650 (72.1)	38,609 (78.3)	0.14
Female sex	68,408 (55.6)	39,956 (57.0)	28,452 (53.7)	0.07	1,846 (50.2)	26,606 (53.9)	0.07
Rural Residence‡							
No	103,141 (83.8)	58,203 (83.0)	44,938 (84.8)	0.05	3,090 (84.1)	41,848 (84.8)	0.02
Yes	19,931 (16.2)	11,892 (17.0)	8,039 (15.2)	0.05	580 (15.8)	7,459 (15.1)	0.02
Oral Anticoagulant Dispensed							
Apixaban	5,890 (4.8)	2,810 (4.0)	3,080 (5.8)	0.08	570 (15.5)	2,510 (5.1)	0.35
Dabigatran	6,608 (5.4)	2,775 (4.0)	3,833 (7.2)	0.14	473 (12.9)	3,360 (6.8)	0.20
Rivaroxaban	51,409 (41.7)	42,546 (60.7)	8,863 (16.7)	1.01	1,150 (31.3)	7,713 (15.6)	0.38
Warfarin	59,232 (48.1)	22,009 (31.4)	37,223 (70.2)	0.84	1,481 (40.3)	35,742 (72.5)	0.69
Indication							
Atrial Fibrillation within 10 yr	62,957 (51.1)	22,530 (32.1)	40,427 (76.3)	0.99	2,988 (81.3)	37,439 (75.9)	0.13
Joint replacement within 35 d	44,375 (36.0)	38,939 (55.5)	5,436 (10.3)	1.10	502 (13.7)	4,934 (10.0)	0.11
Major surgery index hospitalization	22,043 (17.9)	17,384 (24.8)	4,659 (8.8)	0.44	590 (16.1)	4,069 (8.2)	0.24
Active cancer within 180 d	7,858 (6.4)	3,548 (5.1)	4,310 (8.1)	0.12	278 (7.6)	4,032 (8.2)	0.02
DVT or PE index hospitalization	6,407 (5.2)	1,783 (2.5)	4,624 (8.7)	0.27	349 (9.5)	4,275 (8.7)	0.03
Discharging Physician Specialty‡							
Internal medicine	18,490 (15.0)	8,231 (11.7)	10,259 (19.4)	0.21	628 (17.1)	9,631 (19.5)	0.06
Hematologist	1,029 (0.8)	622 (0.9)	407 (0.8)	0.01	30 (0.8)	377 (0.8)	0.01
Cardiologist	13,137 (10.7)	6,856 (9.8)	6,281 (11.9)	0.07	679 (18.5)	5,602 (11.4)	0.20
Orthopedic surgery	31,935 (25.9)	27,860 (39.7)	4,075 (7.7)	0.81	319 (8.7)	3,756 (7.6)	0.04
Family physician	30,694 (24.9)	11,773 (16.8)	18,921 (35.7)	0.44	1,057 (28.8)	17,864 (36.2)	0.16
Other	27,776 (22.6)	14,786 (21.1)	12,990 (24.5)	0.08	957 (26.0)	12,033 (24.4)	0.04
Prescribing Physician Specialty‡							
Family Medicine	41,524 (33.7)	12,604 (18.0)	28,920 (54.6)	0.82	1,274 (34.7)	27,646 (56.0)	0.44
Orthopedic surgery	31,394 (25.5)	28,014 (39.9)	3,380 (6.4)	0.87	287 (7.8)	3,093 (6.3)	0.06
Internal Medicine	9,958 (8.1)	5,350 (7.6)	4,608 (8.7)	0.04	432 (11.8)	4,176 (8.5)	0.11
Cardiologist	7,083 (5.8)	3,840 (5.5)	3,243 (6.1)	0.03	441 (12.0)	2,802 (5.7)	0.22
Hematologist	2,324 (1.9)	1,808 (2.6)	516 (1.0)	0.12	107 (2.9)	409 (0.8)	0.15
Other	8,792 (7.1)	4,843 (6.9)	3,949 (7.5)	0.02	387 (10.5)	3,562 (7.2)	0.12
Unknown	22,064 (17.9)	13,681 (19.5)	8,383 (15.8)	0.10	746 (20.3)	7,637 (15.5)	0.13
Past Medical History							
Hospitalizations within 1 yr†	0.67 ± 1.16	0.30 ± 0.73	1.16 ± 1.42	0.76	0.99 ± 1.32	1.17 ± 1.43	0.13
Thromboembolic events	13,741 (11.2)	10,483 (19.8)	3,258 (4.6)	0.48	730 (19.9)	9,753 (19.8)	0.00

within 3 yr							
Ischemic stroke	4,419 (3.6)	990 (1.4)	3,429 (6.5)	0.26	228 (6.2)	3,201 (6.5)	0.01
Transient ischemic stroke	2,757 (2.2)	853 (1.2)	1,904 (3.6)	0.16	142 (3.9)	1,762 (3.6)	0.02
Peripheral vascular disease event	2,540 (2.1)	680 (1.0)	1,860 (3.5)	0.17	106 (2.9)	1,754 (3.6)	0.04
Systemic embolism	705 (0.6)	155 (0.2)	550 (1.0)	0.10	34 (0.9)	516 (1.0)	0.01
PE	2,393 (1.9)	349 (0.5)	2,044 (3.9)	0.23	152 (4.1)	1,892 (3.8)	0.02
DVT	3,280 (2.7)	580 (0.8)	2,700 (5.1)	0.25	204 (5.6)	2,496 (5.1)	0.02
Hemorrhagic event within 3 yr	13,406 (10.9)	3,627 (5.2)	9,779 (18.5)	0.42	616 (16.8)	9,163 (18.6)	0.05
Intracranial bleeding	777 (0.6)	230 (0.3)	547 (1.0)	0.09	27 (0.7)	520 (1.1)	0.03
Upper gastrointestinal bleeding	3,830 (3.1)	1,068 (1.5)	2,762 (5.2)	0.21	182 (5.0)	2,580 (5.2)	0.01
Lower gastrointestinal bleeding	1,498 (1.2)	453 (0.6)	1,045 (2.0)	0.12	85 (2.3)	960 (1.9)	0.03
Other major bleeds	8,750 (7.1)	2,132 (3.0)	6,618 (12.5)	0.36	392 (10.7)	6,226 (12.6)	0.06
Comorbidities							
Congestive heart failure	47,133 (38.3)	14,265 (20.3)	32,868 (62.0)	0.93	2,096 (57.0)	30,772 (62.4)	0.11
Hypertension	106,292 (86.3)	57,447 (81.9)	48,845 (92.2)	0.31	3,378 (91.9)	45,467 (92.2)	0.01
Diabetes	46,522 (37.8)	22,569 (32.2)	23,953 (45.2)	0.27	1,627 (44.3)	22,326 (45.3)	0.02
Renal dysfunction□	11,216 (9.1)	2,491 (3.6)	8,725 (16.5)	0.44	418 (11.4)	8,307 (16.8)	0.16
Liver dysfunction□	1,349 (1.1)	343 (0.5)	1,006 (1.9)	0.13	68 (1.9)	938 (1.9)	0.00
Drug abuse	14,226 (11.6)	11,642 (16.6)	2,584 (4.9)	0.39	202 (5.5)	2,382 (4.8)	0.03
Alcohol abuse-past 3 yr	1,401 (1.1)	517 (0.7)	884 (1.7)	0.09	64 (1.7)	820 (1.7)	0.01
Charlson Score							
0	20,946 (17.0)	11,714 (16.7)	9,232 (17.4)	0.02	669 (18.2)	8,563 (17.4)	0.02
1	14,766 (12.0)	6,041 (8.6)	8,725 (16.5)	0.24	637 (17.3)	8,088 (16.4)	0.03
2+	32,563 (26.4)	8,967 (12.8)	23,596 (44.5)	0.75	1,355 (36.9)	22,241 (45.1	0.17
N/A (No hospitalization)	54,864 (44.6)	43,418 (61.9)	11,446 (21.6)	0.90	1,013 (27.6)	10,433 (21.2)	0.15
CHADS2-VASC Score							
Mean ± SD†	4.08 ± 1.59	3.49 ± 1.37	4.86 ± 1.53	0.95	4.77 ± 1.47	4.87 ± 1.53	0.07
Median (IQR)	4 (3-5)	3 (3-4)	5 (4-6)	0.98	5 (4-6)	5 (4-6)	0.07
HAS-B_ED Score							
Mean ± SD†	2.20 ± 0.68	2.09 ± 0.63	2.36 ± 0.71	0.41	2.30 ± 0.69	2.37 ± 0.72	0.09
Median (IQR)	2 (2-3)	2 (2-2)	2 (2-3)	0.38	2 (2-3)	2 (2-3)	0.10
Concomitant Medications within 120 d							
NSAID	19,273 (15.7)	15,344 (21.9)	3,929 (7.4)	0.42	304 (8.3)	3,625 (7.3)	0.03
Aspirin	2,870 (2.3)	2,212 (3.2)	658 (1.2)	0.13	41 (1.1)	617 (1.3)	0.01
Other Antiplatelet	7,026 (5.7)	4,459 (6.4)	2,567 (4.8)	0.07	207 (5.6)	2,360 (4.8)	0.04
Amiodarone	4,048 (3.3)	598 (0.9)	3,450 (6.5)	0.30	242 (6.6)	3,208 (6.5)	0.00
SSRI	14,864 (12.1)	6,189 (8.8)	8,675 (16.4)	0.23	428 (11.6)	8,247 (16.7)	0.15
Antibiotic within 30 d	17,345 (14.1)	7,384 (10.5)	9,961 (18.8)	0.24	541 (14.7)	9,420 (19.1)	0.12

* reported as number (%) unless otherwise indicated; § Standardized difference; † Mean (standard deviation); ‡data missing for < 0.07%; IQR = interquartile range; DVT = deep vein thrombosis; PE = pulmonary embolism; NSAID = Nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor; □Abnormal renal function included ICD-10 codes for dialysis, chronic renal disease, renal cancer, renal surgery; Abnormal liver disease included ICD-10 codes for cirrhosis, chronic liver disease, liver cancer, hepatitis, liver surgery

Table 3. Outcome Event Rates Over Time Post-hospital Discharge*

Hemorrhages	N = 8767	Event Rates		
		Over 1 year	First 30 Days	After 30 Days
Overall		17.7 [17.4,18.1]	25.8 [24.8,26.8]	15.7 [15.3,16.1]
Intracranial bleed	664 (7.6)	1.3 [1.2,1.4]	1.2 [1.0,1.4]	1.4 [1.3,1.5]
Upper GI bleed	2,392 (27.3)	4.8 [4.6,5.0]	7.5 [7.0,8.0]	4.2 [4.0,4.4]
Lower GI bleed	669 (7.6)	1.4 [1.3,1.5]	1.9 [1.6,2.2]	1.2 [1.1,1.3]
Other major bleed	5,042 (57.5)	10.2 [9.9,10.5]	15.3 [14.5,16.0]	8.9 [8.6,9.2]
Incident Users	3,312 (37.8)	14.6 [14.1,15.1]	21.9 [20.7,23.1]	12.1 [11.6,12.7]
Prevalent Users	5,455 (62.2)	20.4 [19.9,20.9]	31.1 [29.4,32.8]	18.4 [17.8,18.9]
Non-switchers	5,044 (92.5)	20.5 [19.9,21.0]	31.2 [29.5,32.9]	18.4 [17.8,19.0]
Switchers	411 (7.5)	19.6 [17.7,21.5]	29.5 [23.4,35.7]	18.0 [16.0,19.9]
Male	4677 (53.3)	21.4 [20.8,22.0]	32.1 [30.5,33.8]	18.7 [18.0,19.3]
Female	4090 (46.7)	14.8 [14.4,15.3]	20.8 [19.6,22.0]	13.3 [12.9,13.8]
Thromboembolic Events	**Number (%)**	**Event Rates**		
	N = 4643	**Over 1 year**	**Within First 30 Days**	**After 30 Days**
Overall		9.4 [9.1,9.7]	19.3 [18.4,20.2]	6.9 [6.6,7.1]
Ischemic Stroke	1,001 (21.6)	2.0 [1.9,2.2]	2.8 [2.5,3.2]	1.8 [1.7,2.0]
TIA	542 (11.7)	1.1 [1.0,1.2]	1.5 [1.2,1.7]	1.0 [0.9,1.1]
PVD	789 (17.0)	1.6 [1.5,1.7]	1.9 [1.6,2.1]	1.5 [1.4,1.7]
Systemic Embolism	153 (3.3)	0.3 [0.3,0.4]	0.6 [0.5,0.8]	0.2 [0.2,0.3]
Pulmonary Embolism	978 (21.1)	2.0 [1.9,2.1]	6.4 [5.9,6.9]	0.9 [0.8,1.0]
DVT	1,180 (25.4)	2.4 [2.3,2.5]	6.2 [5.7,6.7]	1.4 [1.3,1.5]
Incident Users	2274 (49.0)	10.0 [9.6,10.4]	21.4 [20.2,22.6]	6.2 [5.8,6.7]
Prevalent Users	2369 (51.0)	8.9 [8.5,9.2]	16.5 [15.3,17.7]	7.4 [7.0,7.8]
Non-switchers	205 (4.4)	9.8 [8.5,11.1]	23.8 [18.3,29.4]	7.5 [6.2,8.7]
Switchers	2164 (46.6)	8.8 [8.4,9.2]	16.0 [14.7,17.2]	7.4 [7.0,7.8]
Male	2193 (47.2)	10.0 [9.6,10.5]	21.4 [20.0,22.7]	7.1 [6.8,7.5]
Female	2450 (53.8)	8.9 [8.5,9.2]	17.7 [16.6,18.8]	6.7 [6.3,7.0]

* reported as number (%) and event rates as per 100 person-years (95% CI)

Figure 1. Participant selection flowchart

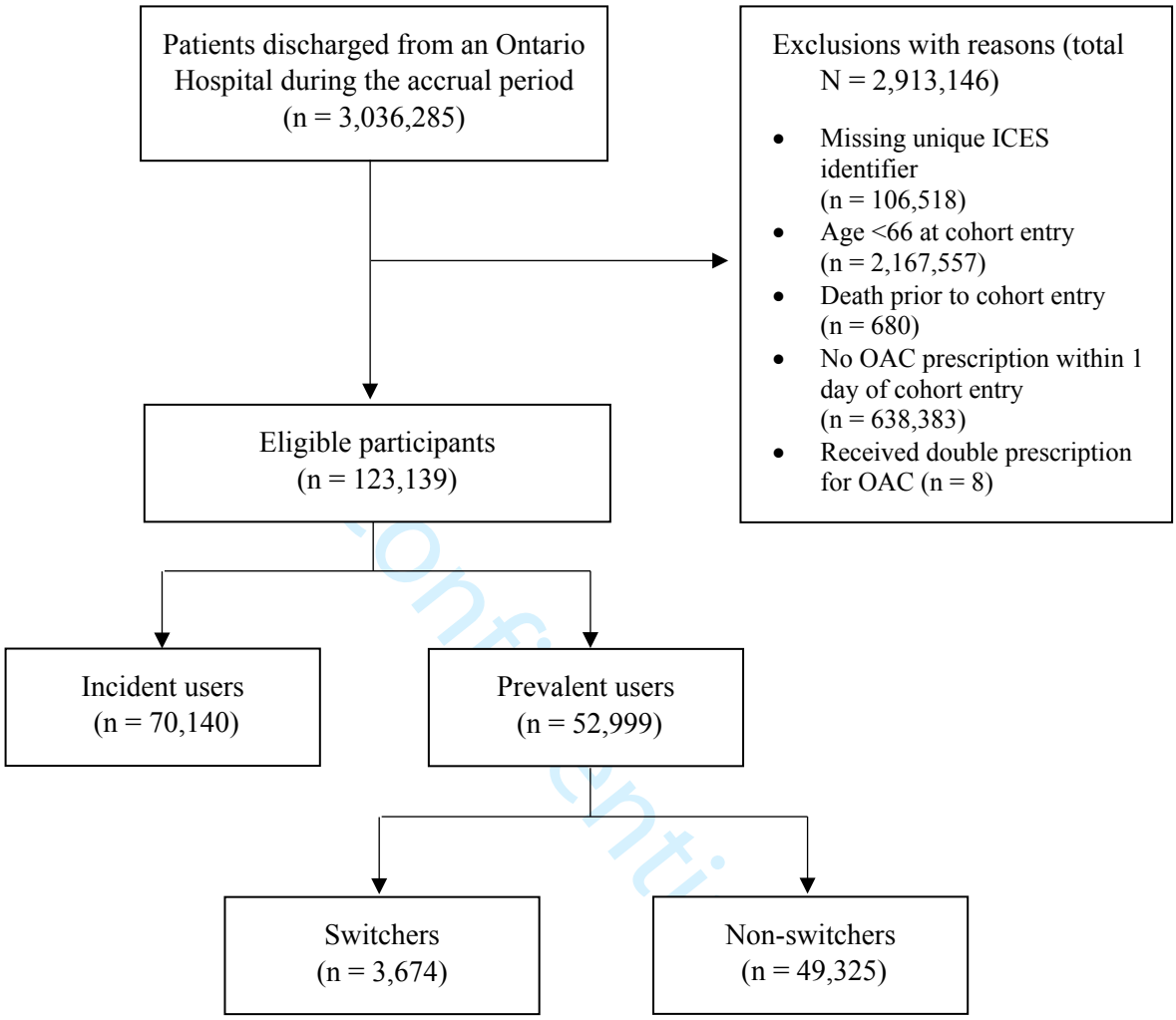


Figure 2. Cohort Timelines and Definitions

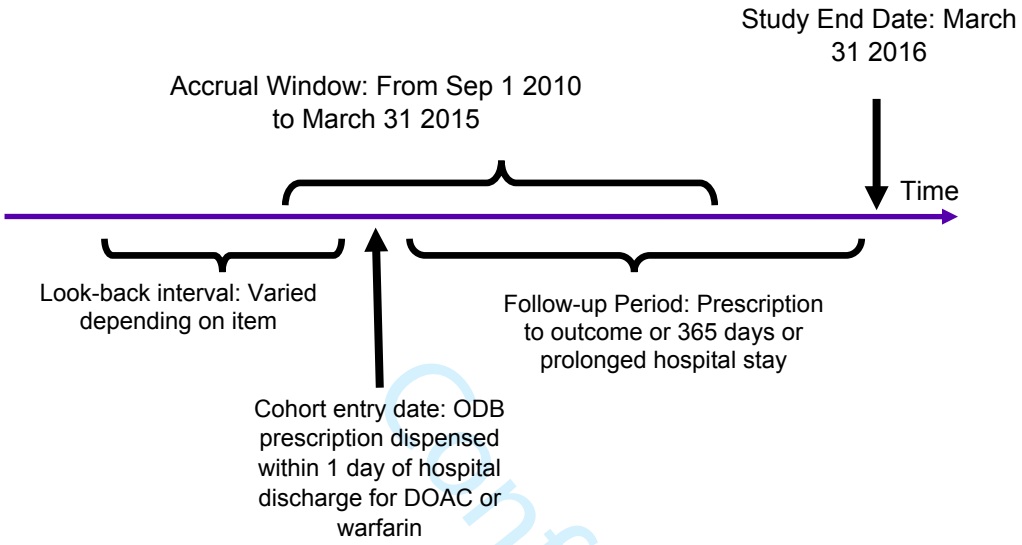


Figure 3. Hemorrhage Event Rates Post-Hospital Discharge

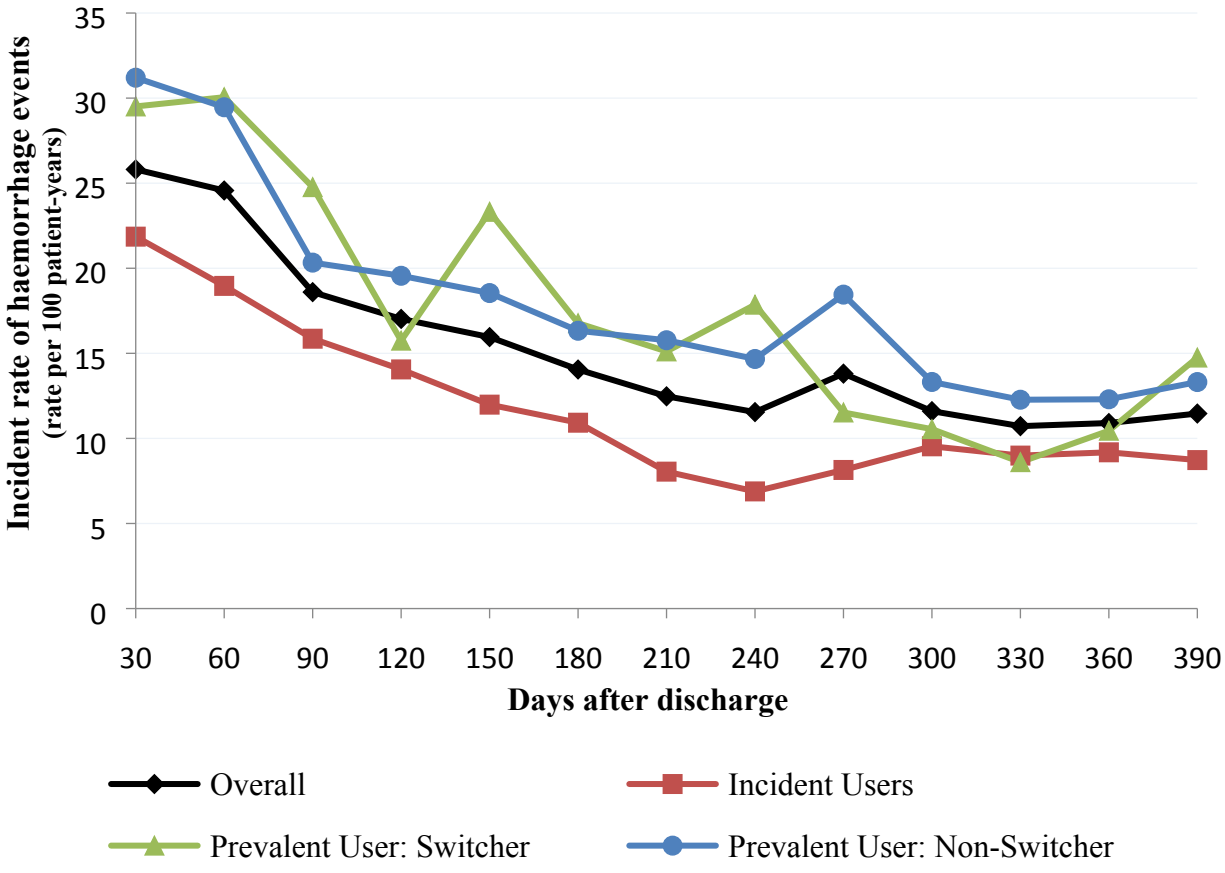
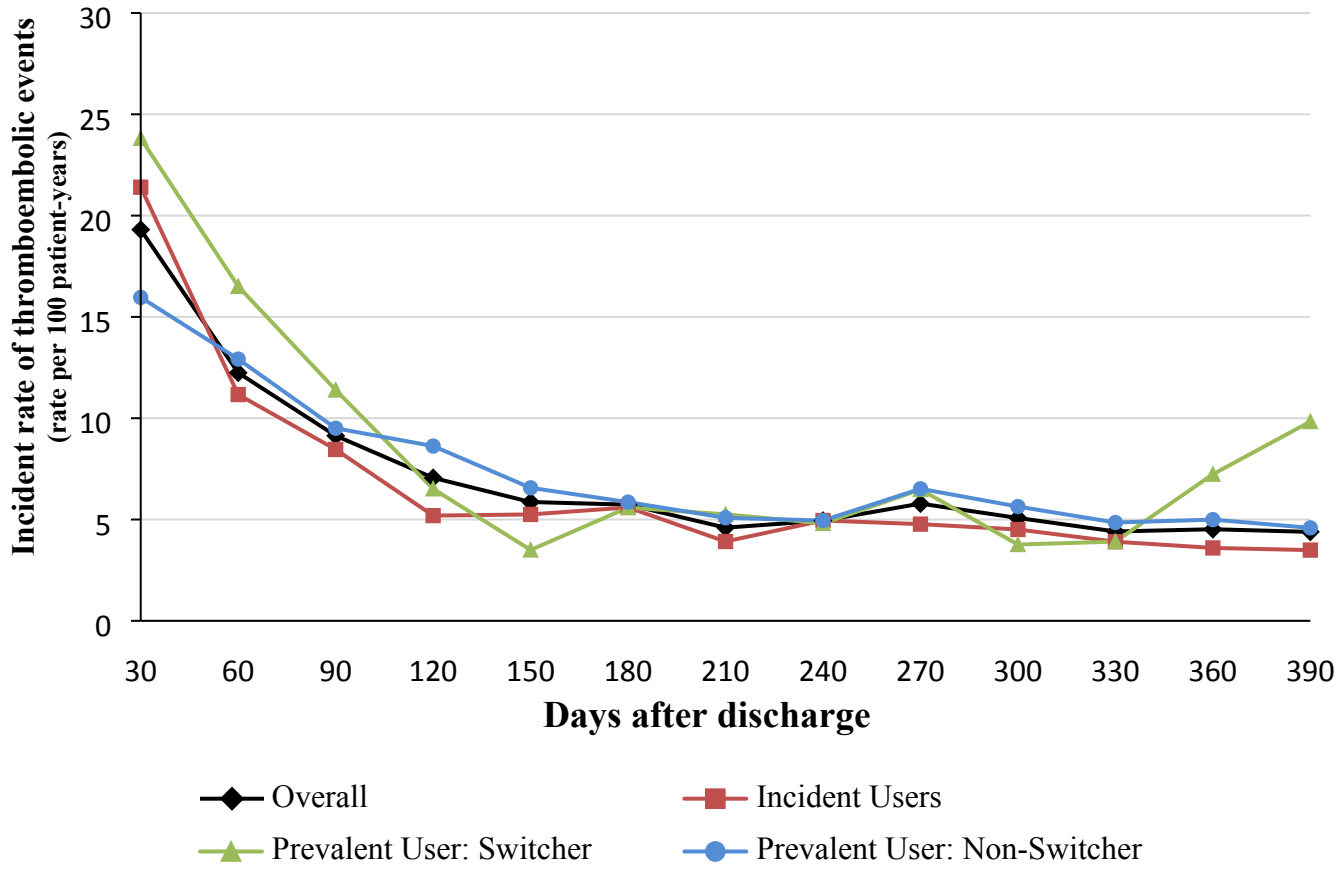


Figure 4. Thromboembolic Event Rates Post-Hospital Discharge



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Reporting checklist for *OAC Post-discharge Events. Holbrook et al.*

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3

Methods

Study design	#4	Present key elements of study design early in the paper	3-4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/A – this is a single arm cohort
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	4 (attempts to minimize selection

			bias, missing data bias
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5
Statistical methods	#12c	Explain how missing data were addressed	6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	5 – multiple categories for follow-up reported including vital status
Statistical methods	#12e	Describe any sensitivity analyses	5 – our statistical analyses include different key subgroups and their event rate.

			This is a type of sensitivity analysis
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6
Participants	#13b	Give reasons for non-participation at each stage	13
Participants	#13c	Consider use of a flow diagram	13
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	10-11
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	10-11
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	14

Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	12
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A – descriptive analysis
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	#18	Summarise key results with reference to study objectives	7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	7

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	8
Generalisability	#21	Discuss the generalisability (external validity) of the study results	7
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8