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Research

Time trends in intracranial bleeding associated with direct oral anticoagulants: a 5-year cohort study

Kerstin Hogg MBChB MD, Bharat Bahl MD BSc, Meriem Latrous BSc, Sarina Scaffidi Argentina BSc, Jesse Thompson BSc, Aasil Ayyaz Chatha, Lana Castellucci MD MSc, Ian G. Stiell MD MSc

Abstract

Background: Over the past 5 years, dabigatran, rivaroxaban and apixaban were approved for stroke prevention. Phase III studies have shown a lower risk of intracranial bleeding with these direct oral anticoagulants than with warfarin; however, there is a lack of real-life data to validate this. We analyzed time trends in atraumatic intracranial bleeding from 2009 to 2013 among patients prescribed oral anticoagulants and those not prescribed oral anticoagulants.

Methods: We used ICD-10-CA (enhanced Canadian version of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems) codes to identify all patients with atraumatic intracranial bleeding who presented to our neurosurgical centre (serving a population of more than 1.2 million). Trained researchers extracted data on anticoagulant medications used in the week before diagnosis of the intracranial bleed. Provincial prescription data for oral anticoagulants were obtained from IMS Brogan CompuScript Market Dynamics. The primary outcome was the time trend in incident intracranial bleeds associated with oral anticoagulation during the period 2009–2013. The secondary outcomes were the time trend in intracranial bleeds not associated with oral anticoagulation and the provincial prescribing patterns for oral anticoagulants during the same period.

Results: A total of 2050 patients presented with atraumatic intracranial bleeds during the study period. Of the 371 (18%) prescribed an anticoagulant in the week before presentation, 335 were prescribed an oral anticoagulant. There was an increasing time trend in intracranial bleeding associated with oral anticoagulants (p = 0.009; 6 additional events per year) and in intracranial bleeding not associated with oral anticoagulation (p = 0.06). During 2013, prescriptions for warfarin decreased to 70% of all oral anticoagulant prescriptions in the province, whereas those for dabigatran and rivaroxaban increased to 17% and 12%, respectively.

Interpretation: We observed increasing time trends in intracranial bleeding, both associated with and not associated with oral anticoagulants, over the study period. Although aggregate provincial data showed increased prescribing of oral anticoagulants, other more likely explanations for our findings include an aging population or increasing frailty.

Over the past 5 years, dabigatran, rivaroxaban and apixaban were approved for the prevention of stroke in Canadians with nonvalvular atrial fibrillation. The drugs are attractive alternatives to warfarin because of their fixed dosing and predictable effect, no need for monitoring and freedom from dietary restrictions. In particular, phase III studies have reported a lower risk of intracranial bleeding with these direct oral anticoagulants than with warfarin. In the ROCKET-AF trial (the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), rivaroxaban was associated with intracranial bleeding in 0.8% of patients (over a median of 1.9 yr), as compared with 1.2% of patients given warfarin.[1] A meta-analysis of trials comparing dabigatran with warfarin in both atrial fibrillation and venous thrombosis (n = 27 419) showed a decreased risk of intracranial bleeding with dabigatran (relative risk 0.34, 95% confidence interval [CI] 0.25–0.48) compared with warfarin.[2] In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, the rate of intracranial bleeding among patients taking apixaban was 0.3 per 100 patient-years, as compared with 0.8 per 100 patient-years with warfarin.[3]

In contrast, recent press interest has suggested a high risk of bleeding with these direct oral anticoagulants.[4] The Adverse Event Reporting System of the US Food and Drug Administration (FDA) reported that a quarter of adverse events associated with dabigatran use were related to a bleeding event and

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Correspondence to: Kerstin Hogg, dewitk@mcmaster.ca

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that there were more reported bleeding-related deaths with dabigatran (348/2347) than with warfarin (46/647).[5] This difference raised the question of whether patients prescribed direct oral anticoagulants differ from those enrolled in the phase III randomized controlled trials, with a suggestion that in real life, patients with nonvalvular atrial fibrillation are older, have a higher prevalence of renal impairment and are taking more interacting medications compared with those in the trials.[6] Additional data suggest that serum dabigatran levels can vary widely when administered correctly[4] and that off-label prescribing, incorrect dosing and dosage administration errors are not uncommon.[7]

We analyzed time trends in atraumatic intracranial bleeding treated at a Canadian neurosurgical centre during the period when the direct oral anticoagulants were introduced.

Methods

Study design

This study had 2 components. The first was a health records review and the second, a review of provincial prescribing patterns for oral anticoagulants. The study was approved by the Ottawa Health Science Network Research Ethics Board.

The health records review took place in The Ottawa Hospital, a 3-campus hospital with 1149 beds and more than 48 000 admissions per year. The neurosurgical centre provides service to the Champlain Local Health Integration Network (population 1 229 555 as of 2011 census) and receives patients from the entire region. People 65 years or older comprised 14% of the region's population in 2011, and this proportion is predicted to rise to 16% by 2016.[8]

Study cohort

Atraumatic intracranial bleeding was defined as spontaneous intracranial bleeding in any location or a subdural hemorrhage associated with negligible trauma. We excluded traumatic intracranial bleeds, including those encountered in motor vehicle crashes, sporting injuries, assaults, falls outdoors, falls associated with a fracture, falls on stairs or steps, falls on ice in the winter, falls from a height and formal trauma resuscitations. This was a time trend analysis, and we wanted to avoid confounding from a prolonged icy winter with adverse weather conditions, which might lead to a greater number of outdoor falls. We included patients over the age of 50 years who had either spontaneous intracranial bleeding or an isolated subdural bleed associated with a recent fall indoors from a standing height or from a bed. For patients who presented a second time, either because of complications of the initial intracranial bleed (e.g., re-accumulation of a subdural bleed or hydrocephalus) or because of a second bleed, we included only the initial presentation.

Patient encounters were identified in the National Ambulatory Care Reporting System reports from The Ottawa Hospital with the use of ICD-10-CA (enhanced Canadian version of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems) codes for intracerebral, subarachnoid, subdural, epidural, intraventricular and otherwise not specified intracranial bleeding during the period Jan. 1, 2009, to Dec. 31, 2013. Codes were searched in both primary and secondary diagnoses. We included codes for traumatic and atraumatic intracranial bleeding to ensure that we identified all eligible presentations, even those misclassified. Two of us (K.H. and B.B.), both practising physicians, manually searched the electronic records to identify all patients fulfilling the inclusion criteria. An independent second screen was performed during data extraction.

Data collection

Patient age, sex and admission date were available in the hospital health records. The data were extracted from the single hospital electronic database by 4 medical students (M.L., S.S.A., J.T. and A.A.C.), who were familiar with electronic medical records and medical terminology. The students underwent standardized training in person and were presented with written instructions detailing where to look for each data point. Data extraction was practised on a training set. The students were provided with coding rules detailing how to classify each variable for the database. They each worked on an identical Microsoft Access datasheet created by one of us (K.H.), and results were either entered as a continuous number (e.g., serum creatinine level) or categorized into predefined categories. The students were aware that the study was reporting on intracranial bleeding in patients taking antiplatelet and anticoagulant medications, but they were unaware of the study hypothesis or analysis strategy. Two of us (K.H. and B.B.) performed regular reviews of the data extraction process and helped resolve coding problems.

Each patient encounter was evaluated for administration of antiplatelet and anticoagulant medications in the 7 days before diagnosis of the intracranial bleed. This information was extracted from ambulance charts, emergency department nurse and physician charts, inpatient medicine reconciliation charts (recorded by pharmacy using 2 independent sources), operation reports and discharge summaries. When there was no record of an antiplatelet or anticoagulant medication in any of these 6 documents, the patient was considered not to have taken the drug in the 7 days before diagnosis of the bleed. When there was a record of such medication use but the drug was stopped before the 7-day period, the patient was considered not to have taken the drug. Other information extracted from the health records included the site of the intracranial bleed (as per computed tomography scan) and the serum creatinine level (as measured in the emergency department).

The quality of data extraction was assessed by an additional reviewer (B.B.), who re-extracted data from a random sample of 160 patient charts.

For provincial prescribing trends, we obtained monthly prescribing data for oral anticoagulants during the 5-year study period. Ontario prescribing data was obtained from Xu and colleagues,[9] who used data from the IMS Brogan Canadian CompuScript database. We updated the prescription data using the same source. IMS Brogan collects prescribing data from more than 60% of Canadian pharmacies. The data have been used previously to evaluate prescribing trends.[10–12] We

requested further information on data collection; however, IMS Brogan does not release details regarding which pharmacies contribute to their database. Data for the same period were available from both sources and were compared to evaluate consistency of the findings.

Outcome measures

The primary outcome was the time trend in incident intracranial bleeds associated with oral anticoagulation during the period 2009–2013. The secondary outcomes were the time trend in intracranial bleeds not associated with oral anticoagulation and the provincial prescribing patterns for oral anticoagulants during the same period.

Statistical analysis

To account for confounding, we analyzed the time trend in concomitant antiplatelet and oral anticoagulant prescriptions and the presenting serum creatinine levels in patients with anticoagulant-associated bleeds. Poisson regression analysis was applied as a test for time trend by fitting a regression line to the monthly incidence of intracranial bleeding, regressed on year. Poisson regression was chosen as a model that fits the assumption of small independent count data (in this case, the rate). We evaluated the quality of data extraction using the κ coefficient. We used the Mann–Whitney *U* test to compare serum creatinine levels between patients taking warfarin and those taking direct oral anticoagulants (missing data were excluded from analysis).

All data were analyzed with the use of IBM SPSS Statistics 22 software.

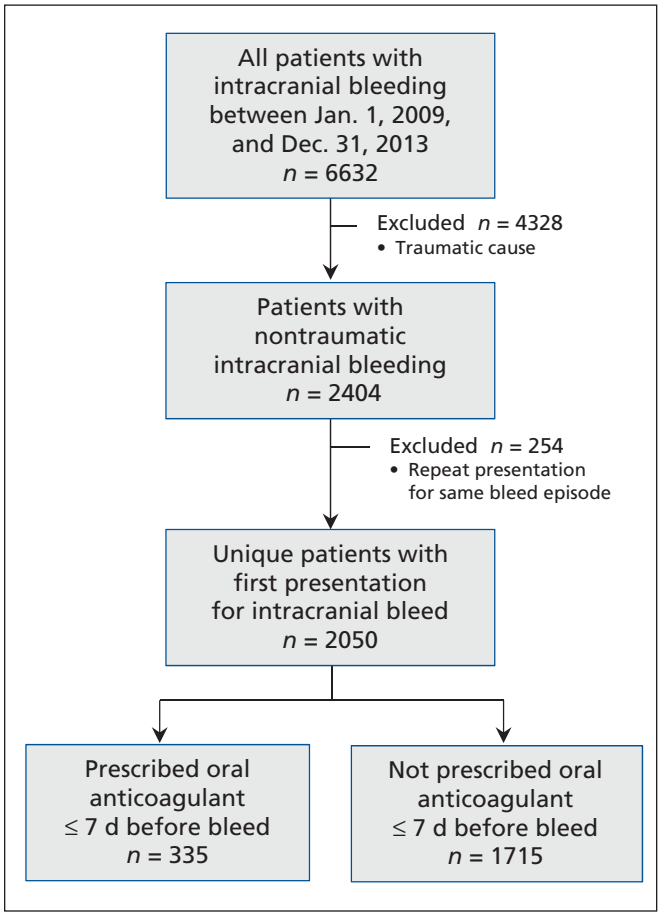

Figure 1: Selection of patients for the study cohort.

Results

During the 5-year study period, a total of 2050 patients presented to the neurosurgical centre with spontaneous intracranial bleeds (Figure 1). All electronic medical records were available. The median patient age was 72 (interquartile range 58–82) years, and 51.5% were male (Table 1). Subdural and intracerebral hemorrhages were the most common, accounting for 73% of all bleeds. Overall, 371 (18.1%) of the patients

Table 1: Characteristics of patients included in the study

Characteristic	No. (%) of patients* n = 2050
Age, yr, median (IQR)	72 (58–82)
Sex, male	1056 (51.5)
Serum creatinine level, μmol/L, median (IQR)†	78 (62–99)
Anticoagulant	
None	1679 (81.9)
Warfarin	315 (15.4)
Dabigatran	16 (0.8)
Rivaroxaban	4 (0.2)
Apixaban	0
Low-molecular-weight heparin	35 (1.7)
Fondaparinux	1 (0.05)
Antiplatelet	
None	1516 (74.0)
Acetylsalicylic acid	436 (21.3)
Clopidogrel	50 (2.4)
Prasugrel	1 (0.05)
Dual antiplatelets	47 (2.3)
Combinations	
Antiplatelet and anticoagulant	94 (4.6)
Antiplatelet or anticoagulant	811 (39.6)
Bleeding site	
Intracerebral	753 (36.7)
Subarachnoid	460 (22.4)
Subdural	750 (36.6)
Epidural	1 (0.05)
Intraventricular	11 (0.5)
≥ 1 site	73 (3.6)

Note: IQR = interquartile range.
*Unless stated otherwise.
†54/2050 patients had no serum creatinine measurement.

were prescribed anticoagulation, 335 of whom received oral anticoagulants, in the week before their hospital presentation. An antiplatelet medication was prescribed to 534 patients (26.0%), and both an anticoagulant and an antiplatelet agent to 86 (4.2%). All data were available except for serum creatinine levels for 54 patients.

There was a 15% increase in the number of patient encounters for intracranial bleeding per year from 2009 to 2013. The number of bleeds involving patients prescribed an oral anticoagulant increased over time ($p = 0.009$), with 6 additional bleeds per year on average. The findings were similar among patients not prescribed an oral anticoagulant, although the upward time trend was not significant ($p = 0.06$) (Figure 2).

The provincial prescribing data showed a decrease in warfarin prescriptions during the study period, and increases in prescriptions for dabigatran, apixaban and rivaroxaban during the same period (Figure 3). As of December 2013, prescriptions for warfarin decreased to 64% of all oral anticoagulant prescriptions in the province, whereas dabigatran accounted for 16% of oral anticoagulant prescriptions, and rivaroxaban and apixaban for 17% and 3%, respectively. The annual number of intracranial bleeds associated with oral anticoagulants are shown in Table 2.

There was no time trend in concomitant antiplatelet and oral anticoagulant prescriptions, nor was one anticoagulant associated with a greater proportion of single or dual antiplatelet therapy. There was no significant difference in the distribution of serum creatinine levels between patients whose bleeds were associated with a direct oral anticoagulant and those with warfarin-associated bleeds. The κ score between data extractors was 0.90 (95% CI 0.89–0.91).

Interpretation

In our neurosurgical centre, we found a significant upward time trend in incident atraumatic intracranial bleeds from 2009 to 2013 among patients prescribed oral anticoagulants. We also observed a nonsignificant upward trend among patients not prescribed oral anticoagulants during the same period. During 2013, 85% of the bleeds associated with oral anticoagulation involved warfarin, 10% dabigatran and 5% rivaroxaban. That same year, dabigatran and rivaroxaban prescriptions accounted for 17% and 12%, respectively, of all oral anticoagulant prescriptions in Ontario, and warfarin for 70%.

We found an increasing trend in the number of bleeding events associated with oral anticoagulants during the time that the direct anticoagulant drugs were introduced. We found that the number of warfarin-associated intracranial bleeds did not fall with the introduction of the direct oral anticoagulants. Xu and colleagues[9] showed that the number of warfarin prescriptions in Ontario stayed the same between 2010 and 2012. A possible explanation is that the overall number of people prescribed oral anticoagulants is increasing each year, but patients taking warfarin are not being switched to a direct oral anticoagulant and, instead, patients newly prescribed anticoagulation are starting with a direct oral anticoagulant. Another explanation may be that more frail and older patients are prescribed an anticoagulant compared with previous practice.

Although prescription of the direct oral anticoagulants increased over the study period, we cannot draw conclusions to associate this change with the increasing trend in intracranial bleeds associated with oral anticoagulation. We found

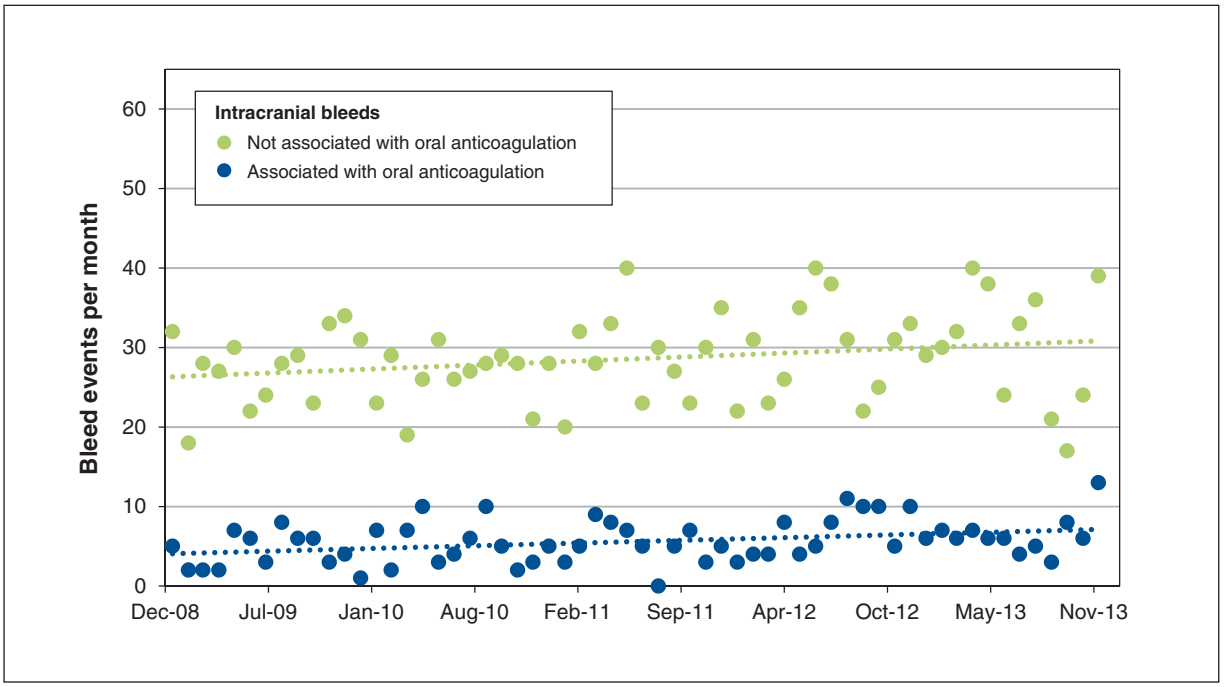

Figure 2: Time trends in atraumatic intracranial bleeding among patients prescribed oral anticoagulants and patients not prescribed oral anticoagulants.

increasing trends in bleeds among patients prescribed oral anticoagulants and those not prescribed oral anticoagulants. This finding may reflect a change in population demographics, and an increasing proportion of older people living in the catchment area of our institution. There was no change in the neurosurgical referral guidelines or in patient management during the study period. Furthermore, the coding department has used ICD-10-CA codes since 2002. Coding was performed by the same group of qualified and dedicated hospital coders throughout the study period.

There has been considerable discussion about the real-life incidence of major bleeding associated with the direct oral anticoagulants. In particular, there has been concern whether patients prescribed direct oral anticoagulants differ from those enrolled in the phase III randomized controlled trials.[6] A recent study showed no increase in major bleeding following the introduction of the direct oral anticoagulants.[13] In May 2014, the FDA published Medicare results for patients over 65 years of age with atrial fibrillation who were newly prescribed warfarin or dabigatran.[14] The reported rate of intracranial bleeding was 0.3 per 100 person-years among patients taking dabigatran and 9.6 per 100 person-years among those taking warfarin. Larsen and colleagues[15] performed a propensity-matched nationwide cohort study comparing dabigatran and warfarin. The absolute rates of intracranial bleeding associated with dabigatran use were 0.3 per 100 person-years with a dose of 110 mg twice daily and 0.1 per 100 person-years with 150 mg twice daily. With warfarin, the rates were 0.7–1.0 per 100 person-years.

Hankey and colleagues[16] re-analyzed the ROCKET-AF data and reported 172 intracranial bleed events. Warfarin use was significantly associated with intracranial bleeding com-

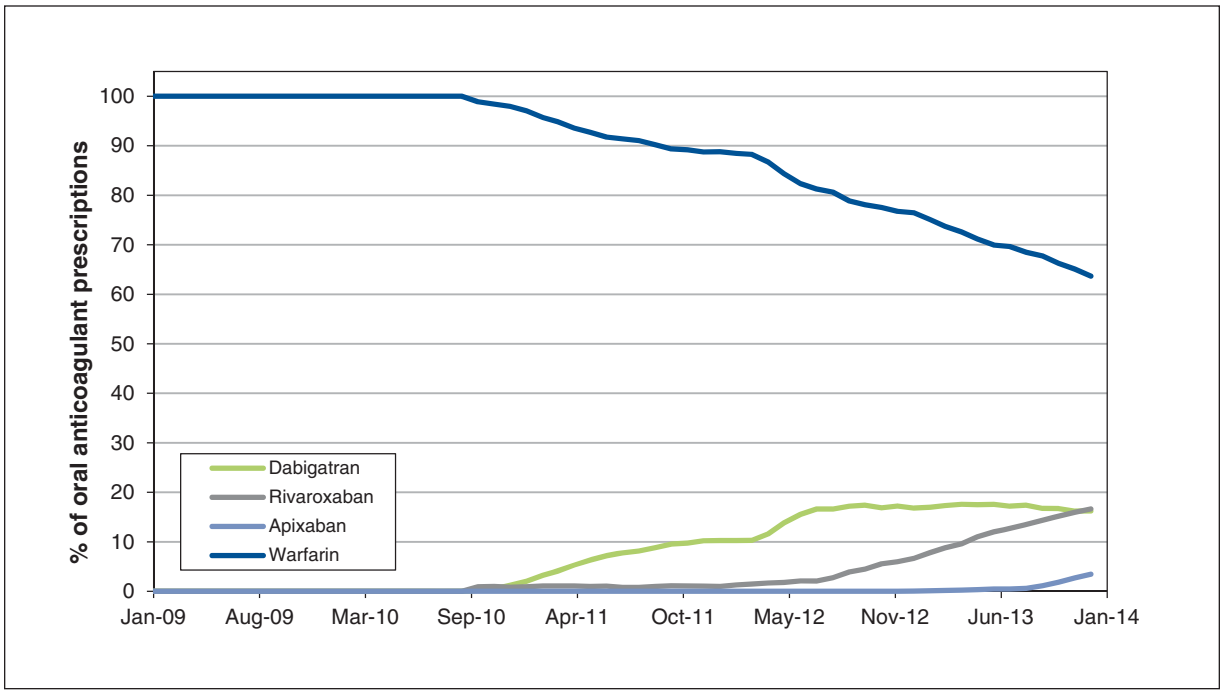

Figure 3: Provincial prescribing patterns for oral anticoagulants in Ontario during the study period.

Table 2: Annual number of spontaneous intracranial bleeds

Variable	2009	2010	2011	2012	2013
Total no. of bleeds	382	378	411	439	440
No. of bleeds not associated with oral anticoagulation	328	318	349	357	363
No. of bleeds associated with oral anticoagulation	54	60	62	82	77
Warfarin	54*	60*	60*	76*	65*
Dabigatran	0	0*	2*	6*	8*
Rivaroxaban	0	0	0*	0*	4*
Apixaban	0	0	0	0	0*

*Period when medication was licensed for prescription.

pared with rivaroxaban. A German registry reported the rates of bleeding among 1776 patients prescribed rivaroxaban between 2011 and 2013.[17] There were 4 cases of intracranial bleeding (0.2%) during a median treatment duration of 274 days. This finding differs from that of a case–control study using US health claims data for propensity-matched patients given warfarin or rivaroxaban for atrial fibrillation.[18] The rate of intracranial bleeding was 1.9 and 1.5 per 100 patient-years for rivaroxaban and warfarin, respectively.

Limitations

Although we report the prescribing patterns for oral anticoagulants in Ontario, we cannot draw conclusions about prescribing patterns in the Champlain region, because we did not have individual patient data. Nor did we have access to data on the number of people living in the province who are prescribed oral anticoagulation.

The Ottawa Hospital provides neurosurgical expertise for the entire Champlain region; however, patients may occasionally be managed in a community hospital with telephone advice from the neurosurgical centre. Although this would have been less likely for patients taking a direct oral anticoagulant, some patients with an intracranial bleed may not have been transferred to our neurosurgical centre and thus not included in the study. If anything, this would have overrepresented patients taking the direct oral anticoagulants.

This was a retrospective study. We made every effort to ensure accuracy of data extraction, especially in regard to anticoagulant exposure; however, a prospective design would have meant greater confidence in the accuracy of data collection.

Although Canada's aging population is growing, the proportion of the population 65 years and older may not be the same as in other developed countries, and therefore our results may not be generalizable to other countries.

Conclusion

Aggregate provincial data showed increased prescribing of direct oral anticoagulants and decreased prescribing of warfarin over the 5-year study period. During that period, we observed an increasing trend in atraumatic intracranial bleeding associated with oral anticoagulant use. However, there was also an increase in intracranial bleeds not associated with oral anticoagulation. Other more likely explanations for these trends include an increasingly elderly population. Future work should focus on individual patient data to explain the increasing number of intracranial bleeds and the absolute risk of intracranial bleeding for patients prescribed direct oral anticoagulants.

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Affiliations: Department of Emergency Medicine (Bahl), Scarborough Hospital, Scarborough, Ont.; Department of Emergency Medicine (Hogg, Latrous, Scaffidi Argentina, Thompson, Chatha, Stiell) and Department of Medicine (Castellucci), University of Ottawa, Ottawa, Ont.

Contributors: Kerstin Hogg conceived the study, obtained ethics approval, liaised with hospital coding and records, designed the study, oversaw the data extraction, analyzed the results and drafted the manuscript. Bharat Bahl supervised the data extraction, performed data extraction and analyzed the results. Meriem Latrous, Sarina Scaffidi Argentina, Jesse Thompson and Aasil Ayyaz Chatha performed the data extraction. Lana Castellucci contributed to data extraction and analysis. Ian Stiell contributed to the study conception and design, and the data analysis. All of the authors were involved in the writing and revising of the manuscript, approved the final version to be published and agreed to act as guarantors of the work.

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