Time trends in intracranial bleeding and the new oral anticoagulants.

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Introduction: Dabigatran, rivaroxaban and apixaban were approved for stroke prevention in the past 4 years. Phase 3 studies reported a lower risk of intracranial bleeding compared to warfarin however there is little real-life data to validate this. We assessed time trends in oral anticoagulant (OAC) associated intracranial bleeding between 2009 and 2013. We compared bleeding rates to provincial OAC prescription trends.

Methods: ICD-10 codes were used to identify all atraumatic intracranial bleeds presenting to our neurosurgical centre (covering a population of 1.3 million). Trained researchers extracted data on anticoagulant medication in the week prior to diagnosis of intracranial bleed. Provincial prescription data for OACs were obtained from IMS Brogan CompuScript Market Dynamics. The primary outcome was the incident OAC-associated intracranial bleed time trend between 2009 and 2013. The secondary outcomes were the non-OAC associated intracranial bleed time trend, and the provincial OAC prescription trends.

Results: 2050 patients presented with atraumatic intracranial bleeds. 371 (18%) patients were prescribed an anticoagulant, of which 335 were OACs. There was an increasing trend over time in the rate of anticoagulant associated bleeding (p=0.009) and non-anticoagulant associated bleeding (p=0.063). Warfarin accounted for a disproportionately large number of all OAC-associated bleeds compared to prescription prevalence. Dabigatran, rivaroxaban and apixaban accounted for a smaller proportion of OAC bleeds when compared to prescription prevalence.

Interpretation: We found an increasing number of patients treated for intracranial bleeding over time. Warfarin accounted for a disproportionate number of intracranial bleeds and the new oral anticoagulants, fewer than expected.

INTRODUCTION

Over the past four years, dabigatran, rivaroxaban and apixaban were approved for stroke prevention in Canadians with non-valvular atrial fibrillation and treatment of venous thromboembolism. The drugs are attractive alternatives to warfarin because of their fixed dosing, predictable effect, lack of monitoring and freedom from dietary restrictions. In particular, the phase 3 studies reported a lower risk of intracranial bleeding compared to warfarin.

In the ROCKET-AF trial rivaroxaban was associated with intracranial bleeding in 0.8% of patients (over a median of 1.9 years), compared with 1.2% of patient on warfarin[1]. A meta-analysis of all the trials comparing dabigatran to warfarin demonstrated the relative risk of intracranial bleeding on dabigatran to be 0.33 compared to warfarin[2]. In ARISTOTLE the rate of intracranial bleeding on apixaban was 0.3 per 100 patient years compared to warfarin, 0.8 per 100 patient years[3].

In contrast, recent press interest has suggested a high risk of bleeding with these drugs[4]. The FDA adverse events registry reported that a quarter of dabigatran adverse events were related to bleeding, and that there were more reported bleeding related deaths with dabigatran than warfarin[5]. This raised the question whether the populations treated with the new oral anticoagulants differ from those enrolled into the randomized controlled trials, with a suggestion that in real life these patients are older, with a higher prevalence of renal impairment and greater co-prescription of interacting medications[6]. Additional data suggests that dabigatran serum levels can vary widely when administered correctly[4] and in reality, off-label prescribing, incorrect dosing, and dosage administration errors are not uncommon[7].

We aimed to establish whether the introduction of the new oral anticoagulants (OACs) was associated with an increase or decrease in the number of OAC-associated intracranial bleeds presenting to a Canadian regional neurosurgical centre.

METHOD

This study had two components. The first part was a health records review and the second, a provincial OAC prescription review. The study was approved by the Ottawa Health Sciences Network research ethics board.

The health records review took place in The Ottawa Hospital, a three campus hospital with 1,149 beds and over 48,000 admissions per year. The neurosurgical centre services the Champlain local health integration network (population 1,229,555 as of 2011 census), and receives patients from the entire region. Seniors comprised 14% of the population in 2011 and this proportion is predicted to rise to 16% by 2016.

Atraumatic intracranial bleeds were defined as spontaneous intracranial bleeding in any location, or a subdural hemorrhage associated with negligible trauma. We excluded traumatic intracranial bleeds such as those encountered in motor vehicle accidents, sporting injuries, assaults, falls outdoors, falls associated with a fracture, falls on stairs or steps, and falls on ice in the winter, falls from a height and formal trauma resuscitations. This avoided confounding from a prolonged icy winter with adverse weather conditions. The inclusion criteria were either spontaneous intracranial bleeding or else an isolated subdural bleed in a patient over the age of 50 associated with a recent fall from standing indoors, or fall from a bed. Each patient was included on their initial presentation visit only.

Patient encounters were identified using the ICD-10 codes for intracerebral, subarachnoid, subdural, epidural, intraventricular and otherwise not specified intracranial bleeding, between 1st January 2009 and 31st December 2013. Two researchers hand searched the electronic records to identify all patients fulfilling the inclusion criteria. An independent second screen was performed during data extraction.

Patient age, sex and admission date was provided by hospital health records. The data were extracted by four trained researchers using a Microsoft Access database. Each patient encounter was evaluated

for administration of antiplatelet medication and anticoagulant medication in the week prior to diagnosis of the intracranial bleed. This information was sourced by reading the ambulance chart, emergency department nurse and physician chart, inpatient medicine reconciliation chart (recorded by pharmacy using two independent sources), operation reports and discharge summary. Site of intracranial bleed and admission serum creatinine were recorded.

Quality of data extraction was assessed by an additional author who re-extracted data from a random sample of 160 patient charts.

Data on the prescription of warfarin, dabigatran, apixaban and rivaroxaban in the province of Ontario was compared to the yearly incidence of OAC-associated atraumatic intracranial bleeding in our institution. We obtained month by month OAC prescribing trends from January 2009 to December 2013. Ontario prescribing data was sourced from Xu *et al*. [8] and IMS Brogan Canadian CompuScript. IMS Brogan collects data from over 60% of Canadian pharmacies. The data has been used previously to evaluate prescriptions tends[9;10;11].

The primary outcome was the incident OAC-associated intracranial bleed time trend between 2009 and 2013. The secondary outcomes were the nonOAC-associated intracranial bleed time trend, and the provincial OAC prescriptions trends. To account for confounding, we analyzed the time trend in antiplatelet/OAC co-prescription, and renal function in patients with OAC-associated bleeds. The data was analyzed in IBM SPSS Statistics 22.

Poisson regression analysis was applied as a test for time trend by fitting a regression line to the monthly intracranial bleed incidence, regressed on year. Quality of data extraction was evaluated using the kappa coefficient. We used the Mann-Whitney U test to compare serum creatinine between the warfarin and the new OAC medications.

RESULTS

Between the dates of 1st January 2009 and 31st December 2013 there were 2050 patients assessed in the hospital for spontaneous intracranial bleeds. The median patient age was 72 (interquartile range 58-82) and 51.5% were male. Table 1 outlines patient demographics. Subdural and intracerebral hemorrhages were the most common, accounting for 73% of all bleeds. Overall, 371 (18%) were prescribed anticoagulation, 335 of which were oral anticoagulants, in the week prior to their hospital presentation. 534 (26%) were prescribed an antiplatelet medication and 86 (4%) were prescribed both an anticoagulant and an antiplatelet agent.

There was a 15% increase in the number of patient encounters per year between 2009 and 2013. The number of patients with an OAC-associated bleed increased with time ($p = 0.009$) as did the number of patients with nonOAC-associated bleeds ($p = 0.063$) (Figure 1).

The proportions of patients prescribed warfarin in Ontario dropped over these five years, and dabigatran, apixaban and rivaroxaban increased (Figure 2). By the end of 2013, dabigatran accounted for 16% of OAC prescriptions, and rivaroxaban and apixaban 17% and 3% respectively. Over the entire study period, warfarin was associated with 94% (95%CI 91-96%) of the OAC-associated bleeds and 89% of all OAC provincial prescriptions. Dabigatran, rivaroxaban and apixaban were associated with 5% (95%CI 3-8%), 1% (95%CI 0-3%) and 0% (95%CI 0-1%) of the OAC-associated bleeds, and 8%, 3% and 0% of the OAC provincial prescriptions respectively. Tables 2 and 3 detail the yearly OAC-associated bleed rates and provincial prescriptions. In 2012 and 2013, warfarin was associated with a disproportionately large share of the OAC-related bleeds, while the newer anticoagulants had a trend towards fewer intracranial bleeds compared to their prescription rates.

There was no time trend in co-prescription of antiplatelet and anticoagulant, nor was one anticoagulant associated with a greater proportion of single or dual antiplatelet therapy. There was no significant difference in the serum creatinine distributions of the new OAC-associated bleeds compared to the warfarin-associated bleeds. The kappa score between data extractors was 0.90 (95%CI 0.89-091).

INTERPRETATION

In our institution between 2009 and 2013, we found a significant upward time trend in incident OAC-associated intracranial bleeds and a non-significant upward trend in nonOAC-associated bleeds. By the end of 2013, dabigatran and rivaroxaban prescriptions accounted for 17% and 12% of all OAC prescriptions. Warfarin was associated with a disproportionate share of the OAC-associated bleeds in 2012 and 2013. We showed a trend towards fewer intracranial bleed events with dabigatran, rivaroxaban and apixaban, in keeping with the Phase 3 study findings.

We found an increasing trend in the number of OAC-related bleeding events during the time that the new anticoagulant drugs were introduced. We found the number of warfarin associated intracranial bleeds did not fall with the introduction of the newer anticoagulant drugs. Xu et al. showed that the number of Ontario warfarin prescriptions stayed the same between 2010 and 2012[8]. One possible explanation is that the overall number of people prescribed OAC is increasing year to year, and that patients who are anticoagulated with warfarin have not changed over to a new anticoagulant. Instead, the patients new to anticoagulation are starting on the new OAC drugs.

There has been considerable discussion around the real life incidence of major bleeding on the new oral anticoagulants. In particular, there has been concern whether the populations treated with the new OACs differs from those enrolled into the randomized controlled trials[6]. Other recent literature has shown no increase in major bleeding following the introduction of the new anticoagulant[12]. In May 2014 FDA published Medicare results for patients over the age of 65 years with atrial fibrillation new to warfarin or dabigatran[13]. The reported rate of intracranial bleeding on dabigatran was 0.3 per 100 person years and 9.6 per 100 person years on warfarin. Larsen et al.[14] performed a propensity matched nation-wide cohort study comparing dabigatran to warfarin. The absolute rates of intracranial

bleed were 0.3 per 100 person years for 110mg bid and 0.1 per 100 person years for 150mg bid. For warfarin the intracranial bleed rates were 0.7-1.0 per 100 person years.

Hankey et al. re-analyzed the ROCKET-AF data and reported 172 intracranial bleed events[15]. Warfarin use was significantly associated with intracranial bleeding compared to rivaroxaban. A German registry reported the rates of bleeding for 1776 patients treated with rivaroxaban between 2011 and 2013[16]. There were four cases of intracranial bleeding (0.2%) during a median treatment duration 274 days. This contrasts to a US health claims database[17] case control study with propensity matched patients treated with warfarin and rivaroxaban for atrial fibrillation. The rate of intracranial bleeding was 1.9 and 1.5 per 100 patient years for rivaroxaban and warfarin respectively.

This study analyzed all atraumatic intracranial bleeds presenting to the neurosurgical centre for a population of 1.3 million, and compared the findings with the OAC prescription trends in Ontario. However, it is possible that some patients diagnosed with an intracranial bleed were not transferred to the neurosurgical centre, and were not identified by this study. This was a retrospective study which was underpowered to prove that the new drugs caused fewer intracranial bleeds than warfarin. We reported the prescription data for the Champlain integrated health network, so local prescribing variation could affect our outcomes.

We found that warfarin accounted for a disproportionate number of intracranial bleeds and the new oral anticoagulants, fewer than expected. These results add to the accumulating evidence that the new OAC medications are less likely to be associated with spontaneous intracranial bleeding than warfarin. Physicians should be reassured by our findings and consider these anticoagulant medications over warfarin in patients who require anticoagulation but have an increased risk of bleeding.

REFERENCES

[1] J.P. Piccini, J. Garg, M.R. Patel, et al. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. *Europ Heart J* 2014; 35:1873-80.

[2] A. Majeed, H.G. Hwang, S.J. Connolly, J.W. et al. Management and Outcomes of Major Bleeding During Treatment With Dabigatran or Warfarin. *Circulation* 2013);128:2325-32.

[3] E.M. Hylek, C. Held, J.H. Alexander, et al. Major Bleeding in Patients With Atrial-áFibrillation Receiving Apixaban or Warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. *J Am Coll Cardiol* 2014;63:2141-7.

[4] T.J. Moore, M.R. Cohen, D.R. Mattison. Dabigatran, bleeding, and the regulators. BMJ 2014;349:g4517.

[5] K.W. McConeghy, A. Bress, D.M. Qato, et al. Evaluation of Dabigatran Bleeding Adverse Reaction Reports in the FDA Adverse Event Reporting System during the First Year of Approval. *Pharmacotherapy* 2014; 3:4561-9.

[6] R. Joppi, E. Cinconze, L. Mezzalira, et al. Hospitalized patients with atrial fibrillation compared to those included in recent trials on novel oral anticoagulants: A population-based study. *Europ J Intern Med* 2013; 24:318-23.

[7] A.S. Larock, F. Mullier, A.L. Sennesael, et al. Appropriateness of Prescribing Dabigatran Etexilate and Rivaroxaban in Patients With Nonvalvular Atrial Fibrillation: A Prospective Study. *Ann Pharmacother* 2014;48:1258-68.

[8] Y. Xu, A.M. Holbrook, C.S. Simpson, et al. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. *CMAJ open* 2013; 1:E115-9.

[9] I. Bayoumi, L. Dolovich, B. Hutchison, A. Holbrook. Medication-related emergency department visits and hospitalizations among older adults. *Can Fam Physician*2014;60: e217-22.

[10] D. Lam, D.A. Gorman, S. Patten, T. Pringsheim. The pharmacoepidemiology of selective serotonin reuptake inhibitors for children and adolescents in Canada from 2005 to 2009: a database analysis. *Paediatr Drugs* 2013;15:319-27.

[11] T. Pringsheim, D.M. Gardner. Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: a descriptive study. *CMAJ open* 2014; 2:E225-32.

[12] M. Badal, M.R. Aryal, J. Mege, et al. Evaluation of Trends of Inpatient Hospitalisation for Significant Haemorrhage in Patients Anticoagulated for Atrial Fibrillation before and after the Release of Novel Anticoagulants. *Heart, Lung and Circ*. 2015;21(1): 94-97.

[13] FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin. http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm .

[14] T.B. Larsen, L.H. Rasmussen, F. Skjøth, et al. Efficacy and Safety of Dabigatran Etexilate and Warfarin in Real-World Patients With Atrial Fibrillation: A Prospective Nationwide Cohort Study. *J Am Coll Cardiol* 2013;61:2264-73.

[15] G.J. Hankey, S.R. Stevens, J.P. Piccini, et al. Intracranial Hemorrhage Among Patients With Atrial Fibrillation Anticoagulated With Warfarin or Rivaroxaban: The Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation. *Stroke* 2014;45:1304-12.

[16] J. Beyer-Westendorf, K. Förster, S. Pannach et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood* 2014;124:55-962.

[17] F. Laliberté, M. Cloutier, W.W. Nelson, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin* 2014;30:1317-25.

Table 1: Demographics of patients

Characteristic	Description	Number or median	% or IQR
Age		72	58-82
Sex	Male	1056	51.5%
Creatinine (μmol/L)		78	62-99
Anticoagulant	None	1679	81.9%
	Warfarin	315	15.4%
	Dabigatran	16	0.8%
	Rivaroxaban	4	0.2%
	Apixaban	0	0.0%
	Low molecular weight heparin	35	1.7%
	Fondaparinux	1	0.0%
Antiplatelet	None	1516	74.0%
	Aspirin	436	21.3%
	Clopidogrel	50	2.4%
	Prasugrel	1	0.0%
	Dual antiplatelets	47	2.3%
Bleeding site	Intracerebral	753	36.7%
	Subarachnoid	460	22.4%
	Subdural	750	36.6%
	Epidural	1	0.0%
	Intraventricular	11	0.5%
	More than one intracranial site	73	3.6%

Table 2: Comparison of individual OAC medication-associated intracranial bleeds

		2009	2010	2011	2012	2013
Total number of intracranial bleeds		382	378	411	439	440
Number of nonOAC bleeds		328	318	349	357	363
Number of OAC-associated bleeds		54	60	62	82	77
OAC as % all OAC-associated bleeds (95% CI)	**Warfarin**	54 100.0% (91.7-100.0%)	60 100.0% (92.5-100.0%)	60 96.8% (87.7-99.5%)	76 92.7% (84.2-97.0%)	65 84.4% (73.9-91.3%)
	Dabigatran	0 0.0%	0 0.0% (0.0-12.3%)	2 3.2% (0.6-12.1%)	6 7.3% (3.0-15.8%)	8 10.4% (4.9-20.0%)
	Rivaroxaban	0 0.0%	0 0.0%	0 0.0% (0.0-7.3%)	0 0.0% (0.1-5.6%)	4 5.2% (1.6-13.2%)
	Apixaban	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0% (0.1-5.9%)

Shaded area = period when medication licensed for prescription

Table 3: Comparison of individual OAC medication prescriptions in Ontario

	2009	2010	2011	2012	2013
Warfarin % OAC prescriptions	100.0%	99.6%	92.1%	82.6%	69.8%
Dabigatran % OAC prescriptions	0.0%	0.2%	6.9%	14.5%	17.1%
Rivaroxaban % OAC prescriptions	0.0%	0.2%	1.0%	2.9%	12.0%
Apixaban % OAC prescriptions	0.0%	0.0%	0.0%	0.0%	1.0%

Shaded area = period when medication licensed for prescription
% = median monthly prescription

Figure 1: Time trend in intracranial bleed events

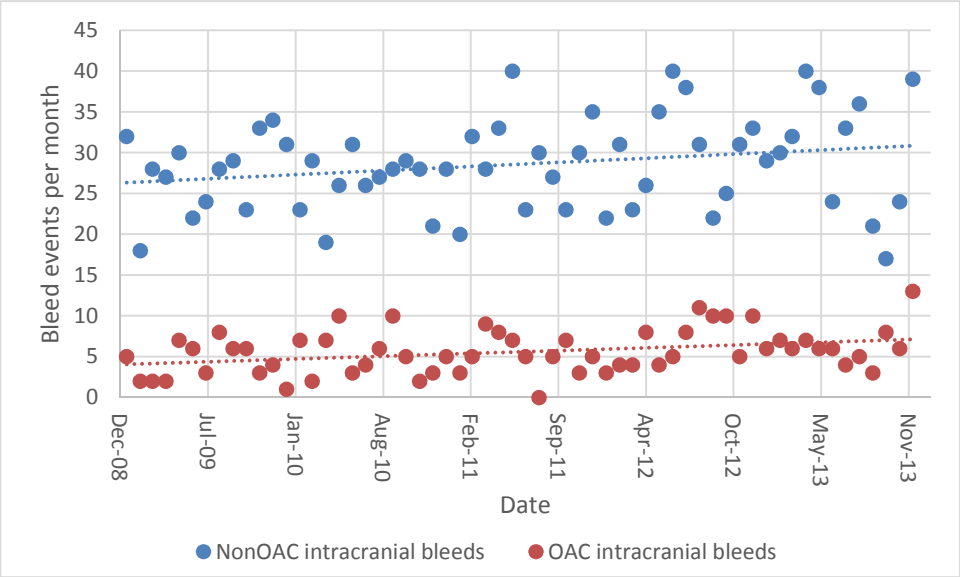

Figure 2: Time trends in Ontario oral anticoagulant prescriptions