Article details: 2015-0037	
Title	Time trends in intracranial bleeding and the new oral anticoagulants: a 5 year cohort.
Authors	Bharat Bahl MD BSc, Meriem Latrous BSc, Sarina Scaffidi Argentina BSc, Jesse Thompson BSc, Aasil Ayyaz Chatha BSc, Lana Castellucci MD MSc, Ian Stiell MD MSc, Kerstin Hogg MBChB, MD
Reviewer 1	Dr. Jeffrey Kline
Institution	Indiana University School of Medicine
General comments (author response in bold)	Authors performed a retrospective study of intracranial hemorrhages at their medical center and found that both non-OAC and OAC-associated ICHs increased with time. Use of new agents is increasing. 1.Methods: a. Consider adding some methodological detail to better describe the training and blinding of abstractors, a description of the two databases and how they are linked. My main concern is ability to report a confidence that you captured all OAC prescriptions. I do not understand the Canadian health system, but perhaps you could reassure the reader that the probability is low that you missed OAC prescriptions. b. Also consider the methodological issues raised in these references (perhaps address points in Figure 1 of Gilbert et al—you have hit most of them): Kaji AH, Schriger D, Green S. Looking through the retrospectoscope: reducing bias in emergency medicine chart review studies. Ann Emerg Med. 2014 Sep;64(3):292-8. Lowenstein SR. Medical record reviews in emergency medicine: the blessing and the curse. Ann Emerg Med. 2005 Apr;45(4):452-5. Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart reviews in emergency medicine research: Where are the methods? Ann Emerg Med. 1996 Mar;27(3):305-8. **Thank you for your thoughtful review.** **We have rewritten two paragraphs in the methods section (pages 7 and 8 of the marked copy) to provide an objective description of the data extraction process. These now read as follows:** **'Patient age, sex and admission date were provided by hospital health records. The data were extracted from the single hospital electronic database by four medical students 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 practiced on a training set. They 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 the first author, and results were entered either as a continuous number (such as the serum creatinine) or else categorized into predefined categories. The students were aware this study was reporting on intracranial bleeding in patients taking antiplatelet and anticoagulant medications, but they were unaware of our hypothesis or analysis strategy. The first and second authors performed regular review of the data extraction process, and helped resolve coding problems.** **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. When there was no record of an antiplatelet or anticoagulant medication in any of these six documents, the patient was considered not to have taken the drug in the prior 7 days. When there was a record of prior medication use, but it had been discontinued prior to the last 7 days, the patient was considered not to have taken the drug. Site of intracranial bleed (as per CT scan) and serum creatinine (as measured in the emergency department) were recorded.'** 2. Results could be strengthened by reporting the entire volume of patients per year, and then the % of these prescribed OACs per year and % with ICH. **Unfortunately we only have patient level data on those who presented with an intracranial bleed at The Ottawa Hospital. We do not have patient level data for anticoagulant prescription. A statement to this effect has been added to the Limitations section, at the top of page 14, which states** **'Although we report the prescribing patterns for oral anticoagulants in Ontario, we cannot draw conclusions about prescribing in the Champlain region as we do not have individual patient data. Nor do we have access to the number of people living in the province who are prescribed oral anticoagulation.'** **A flow diagram of the chart review has been added as Figure 1. This shows the total number of chart initially evaluated and the breakdown of the results.** Can you then clarify if the Poisson adjusts the rate of ICH for total patient volume. I am not a Poisson expert—I just know it is a way of examining small proportions over time. I think it does with the

	offset part of the equation, but would appreciate an explicit statement for the average reader. **Poisson regression is a method for analyzing counts. When regressed on time, it tests for time trends. We did this separately for patients who had an intracranial bleed on an oral anticoagulant, and those who had an intracranial bleed but were not taking an oral anticoagulant. We have added a sentence to the methods section, bottom of page 8, 'Poisson regression was chosen as a model which fits the assumption of small independent count data (in this case, the rate).'** 3. Can you compare slope of OAC vs. non-OAC trend lines in Figure 1? **Following the journal editor requests, we have not performed this comparison and left the results as a description of the intracranial bleeds presenting to the hospital.** 4. In interpretation, not sure I am seeing data to support this statement: "We showed a trend towards fewer intracranial bleed events with dabigatran, rivaroxaban and apixaban, in keeping with the Phase 3 study findings." **This statement has been removed, as has all comparison between the hospital data and the provincial prescribing data.** 5. Can you assign a risk ratio for ICH on a per year basis for warfarin vs. dabigatran and presence or absence of thienopyridenes? I think readers want to know. Warfarin and clopi/pras/ticagrelor risk of bleed vs dabi and clopi/pras/ticagrelor risk of bleed **We would also like to know this information. Unfortunately our prescribing data is population level data for the entire province of Ontario and the intracranial bleed data is individual patient level data from the Champlain region of Ontario. We are unable to link these two sources.**
Reviewer 2	Dr. Alejandro Lazo-Langner
Institution	Department of Medicine, Division of Hematology, University of Western Ontario
General comments (author response in bold)	"Time trends in intracranial bleeding and the new oral anticoagulants: a five year cohort.' The authors present the results of a cohort study of patients admitted to a single center for intracranial bleeding and correlate the data to prescription trends. They report a higher incidence of bleeding associated with warfarin and lower with direct oral anticoagulants. In general the manuscript is well written. However several clarifications need to be made prior to considering this manuscript for publication. 1. How were patients identified? The authors state that they used ICD-10 codes, but where did they get the codes from? Discharge abstracts? (CIHI DAD), NACRS or both? If so, was this the primary diagnosis? secondary diagnosis? **Thank you for your helpful comments. We have responded to each of them in turn.** **We have rewritten paragraph 3 of the Methods section (page 6 of the marked manuscript) as follows 'Patient encounters were identified in the National Ambulatory Care Reporting System reports from The Ottawa Hospital using the ICD-10-CA codes for intracerebral, subarachnoid, subdural, epidural, intraventricular and otherwise not specified intracranial bleeding, between 1st January 2009 and 31st December 2013. Codes were searched in both primary and secondary diagnoses. We included codes for traumatic and atraumatic intracranial bleeding, to ensure we identified all eligible presentations, even those misclassified.'** 2. The authors mentioned briefly that there is a possibility that not all patients with bleeding are referred to their center. This is potential source of bias, and it should be better addressed. **We have rewritten paragraph 2 of the Limitations section (page 14 of the marked manuscript) to read 'The Ottawa Hospital provides neurosurgical expertise for the entire Champlain region, however on occasion, a patient might be managed in a community hospital with telephone advice from the neurosurgical centre. Although this would have been less likely for patients on a new anticoagulant, it is possible that some patients diagnosed with an intracranial bleed were not transferred to the neurosurgical centre, and were not identified. If anything, this would have over-represented patients on the newer anticoagulants.'** 3. Please provide a flow chart describing the process of cohort integration (inclusions/exclusions and

	reasons), if appropriate. **We have created a new Figure 1 which depicts the stages of chart selection and review.** 4. A major concern is the increase in the number of patient encounters for intracranial bleeding. During the study period. This could reflect several situations: 1) there was an increase in the number of prescriptions of anticoagulants (i.e. more people were prescribed anticoagulants); 2) there is a difference in the coding systems used to identify the events of interest (that is, either there was a change in the codes used, or in the way these codes are entered) ; 3) there is indeed an increase in the incidence of intracranial bleeding (which would suppose you have a more susceptible population, something that can be explained by the first point). In the current manuscript there is no mention of any of these concerns. These should be addressed since they might seriously influence the conclusions. 4) What makes me worry about this data is that not only the anticoagulant associated but also the non-anticoagulant associated bleeding events increased, so this makes me think that this might be a reporting issue, or there might be a function of an increase in population numbers. A potential way to deal with this is to standardize your data in reference to the population in your catchment area. **As you have noted, there was an increase in both the number of oral anticoagulant-associated intracranial bleeds and intracranial bleeds not associated with oral anticoagulation. We have rewritten paragraph 3 of the Interpretation section (pages 12 and 13 of the marked manuscript) to read** **'Although prescription of the direct oral anticoagulants increased over these five years, we cannot draw conclusions to associate this change with the increasing trend in oral anticoagulant-associated intracranial bleeds. We found both oral anticoagulant intracranial bleeds and nonoral anticoagulant intracranial bleeds are increasing over time. This may be a reflection of a change in population demographics, and an increasing proportion of elderly people living in the Champlain region. There was no change in the neurosurgical referral guidelines during this time period, nor with patient management. Furthermore, the coding department has used ICD-10-CA coding since 2002. Throughout our study period, the coding was performed by the same group of qualified and dedicated hospital coders.'** **We had reviewed these potential sources of bias at the time of analysis (hospital coding and neurosurgical referral system), and were satisfied that there had been no change over time.** **The most accurate information on population comes from the census data which is available every 5 years. We found it impossible to obtain accurate population data year by year.** 5. Authors present data of provincial prescriptions for anticoagulants and argue that the number of bleeding events related to the prescription numbers, are lower for direct oral anticoagulants. A potential (very rough) way to present this data could be to present ratios of the frequency of bleeding (associated to a specific drug) compared to the percent of prescriptions for that drug. If you do this, you will see that there is an increase in the ratios for all drugs (except apixaban probably because there are not enough patients). Furthermore, the increase in dabigatran related bleedings between 2012 and 2013 is 3.1% after only a marginal increase in the % of dabigatran prescriptions which is worrisome. The ratios of warfarin bleeding compared to the percent of prescriptions are higher than those for other anticoagulants, BUT the data on prescriptions is aggregate provincial data and there might be very different prescriptions patterns between different LHINs and even within the same LHIN between community based and academic practices. This has not been accounted for except very briefly in the discussion and has big implications for this analysis. **We have removed all comparisons between the provincial prescribing data and the hospital intracranial bleed data.** 6. Your conclusions regarding warfarin being associated with a disproportionate share of bleedings in 2012 and 2013 just reflects the fact that is the most widely used anticoagulant. Furthermore you cannot state that you found a trend toward lower proportion of bleeding with direct oral anticoagulants since you do not have the data to support this, even though this might well be the case. The only way to assert this would be to have information on the number of patients prescribed anticoagulants and their follow up. **As for number 5, we have removed all comparison data and conclusions relating to the comparison. The conclusion now reads** **'Direct oral anticoagulant prescribing increased and warfarin prescribing decreased over this five year study. During that period, anticoagulant-associated intracranial bleeds increased in number. However there was also an increase in nonanticoagulant-associated intracranial bleeds and there are likely other causes for this trend, such as an increasingly elderly population. Future work should focus on individual patient data, in order to explain the increasing number of intracranial bleeds, and the absolute risk of intracranial bleeding on the direct oral anticoagulants.'** 7. Please clarify how you determined the number of expected bleedings associated to direct oral anticoagulants.

	As for questions 5 and 6, this comparison has been removed from the paper. **Also please change the term new oral anticoagulants to direct oral anticoagulants which reflects the recent position statement from ISTH.** **All references to NOACs have been changed to 'direct oral anticoagulants'.** 8. Please provide data in table 1 regarding patients with a prescription for either an anticoagulant OR an antiplatelet agent. **We have amended table 1 to show the proportion of patients prescribed either an anticoagulant or and antiplatelet, and both an anticoagulant and an antiplatelet.** 9. Please refer to the STROBE statement to verify key elements to include in observational studies **A completed STROBE form has been uploaded.**
Reviewer 3	Dr. Vicky Tagalakis
Institution	Jewish General Hospital-Sir Mortimer B. Davis, McGill University Center for Clinical Epidemiology & Community Studies
General comments (author response in bold)	This is an interesting study that describes trends in intracranial bleeds with warfarin and the new OACs in a real world setting. The paper is for the most part well written and succinct. There are few grammatical errors. However there are several issues that must be addressed. 1. The authors need to clarify why excluding falls on ice in the winter would avoid confounding from a prolonged icy winter **Thank you for your detailed and helpful comments. We have responded to each comment in turn and now have an improved paper.** **You are right that this statement was not self-explanatory. We have added to the methods section (page 6 of the marked manuscript) to read** **'This was a time trend analysis, and we wished to avoid confounding from a prolonged icy winter with adverse weather conditions which might lead to a greater number of outdoor falls.'** 2. Introduction: more details required on the meta-analysis of all trials that compared dabigatran to warfarin. How many patients were included in the meta-analysis and the 95% CI around the RR of 0.33 should also be included. Did this meta-analysis include afib and VTE trials? Did these trials differentiate between traumatic and atraumatic intracranial bleeds? **None of the trial reported traumatic bleeds separately from atraumatic bleeds.** **We have elaborated on the study by Majeed et al., page 4 of the marked manuscript, first paragraph,** **'A meta-analysis of all the trials comparing dabigatran to warfarin in both atrial fibrillation and venous thrombosis (27,419 patients) demonstrated the relative risk of intracranial bleeding on dabigatran to be 0.34 (95% confidence intervals 0.25-0.48) compared to warfarin.'** 3. Introduction: with regard to the FDA report on bleeding due to dabigatran, were these intracranial bleeds? GI bleeds or any type of bleeding. Moreover, can the authors provide the absolute number of bleeds as per the FDA report. **We have amended the reference to this paper to read 'The FDA adverse events registry reported that a quarter of dabigatran adverse events were related to a bleeding event, and that there were more reported bleeding related deaths with dabigatran (348/2347) than warfarin (46/647)'.** **They report did not differentiate between types of bleed.** 4. Introduction: the authors mention that in real life there is a greater co-prescription of interacting medications. However, the new OACs compared to warfarin are less likely to have drug-drug interactions. **We have clarified that the comparison is between the drug trial patients and those in real-life, not the NOACs and warfarin. Second paragraph, page 4 reads** **'This raised the question whether the populations treated with the direct 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 than observed in the trials.'** 5. Page 5, line 52: It is not clear if patients were excluded from study during data extraction. If so, this needs to be clear and moreover a figure describing the number of patients excluded and for which reason should be provided **Figure 1 now contains a flow diagram of the chart evaluation for inclusion and exclusion.**

	6. Page 6, line 28: the authors state that the Ontario prescribing data was sourced from Xu et al. However Xu et al only describe prescribing patterns for atrial fibrillation. However, this study included patients with VTE and atrial fibrillation. How generalizable is therefore the data sourced from Xu et al to this study. Moreover, the authors should describe the IMS Brogan Cdn CompuScript and what type of Canadian pharmacies are included (since only 60% are captured). **We have removed the comparison between provincial prescriptions and intracranial bleeds. The data for intracranial prescriptions is presented in graphical form only.** **We obtained the prescribing trends for oral anticoagulants in Ontario from both Xu et al. and the company IMS Brogan. We then compared the overlapping data available from both sources (6 months of data). Both were provided in the form % all oral anticoagulants prescribed per month. The two sources agreed to within 0.5%. Therefore, we were comfortable using Xu et al. data initially, followed by the data direct from IMS Brogan.** **We sent emails to and called IMS Brogan, requesting information on their participating pharmacies. Unfortunately, they did not provide us with this data. We have amended paragraph 2, page 8 of the marked manuscript to read** **'The authors requested further information on data collection, however IMS Brogan does not release details regarding which pharmacies contribute to their data. Data for the same time period were available from both sources and were compared to evaluate consistency in the findings.'** 7. Page 6; line 35: The primary outcome is incident OAC-associated intracranial bleed. But it is unclear why this this is the case. Were patients with a prior history of OAC related intracranial bleed excluded. **This point has been clarified at the bottom of page 6 of the Methods section.** **'Patients were included when they presented with a new intracranial bleeding episode. They were excluded if they presented for a second time with complications of the initial intracranial bleed (such re-accumulation of a subdural bleed or hydrocephalus).'** 8. Page 6; line 42. How was renal function measured? **We have amended the sentence at the top of page 8 of the marked manuscript.** **'Site of intracranial bleed (as per CT scan) and serum creatinine (as measured in the emergency department) were recorded.'** 9. Page 7; authors should provide indication for OAC prescription (afib, metallic valve, VTE, etc) **We did not extract data on indication for anticoagulation for the patients who had an intracranial bleed. Nor was this available to us from the provincial prescribing data.** 10. The duration of OAC prescription should also be included (how many days/months were patients using OAC) and for warfarin users the mean INR value in the week prior to hospital presentation should also be included. **We recorded all anticoagulants prescribed during the 7 days prior to bleed. We did not have access to data an accurate length of anticoagulation since many patients are started on anticoagulation in the community by an outside office or their family practitioner. Nor did we have access to INR measurements from the community. For this reason we did not extract any INR values.** **In addition, were any patients being "bridged" at the time of intracranial bleed. This information is important given that bleeding risk on OAC is highest during initiation of OAC and during periods of bridging.** **No patient was being bridged at the time of their bleed.** 11. Page 7 line 23: please clarify what type of patient encounters increased by 15% during the study period. Any type of intracranial bleeds or atraumatic bleeds specifically. **This has been clarified as 'There was a 15% increase in the number of patient encounters for intracranial bleeding per year between 2009 and 2013.'** 12. Page 7, lines 45-52. It is not clear to me how the data in Table 2 and 3 show that new OACs had a trend toward fewer intracranial bleeds compared to their prescription rates. Was this trend significant compared to that of warfarin? **We have removed all comparisons between prescription of oral anticoagulation and intracranial bleeding events on anticoagulation. We have left the analysis of time trends for the number of OAC-associated intracranial bleeds and the nonOAC-associated intracranial bleeds.** 13. Page 8; what is meant by serum creatinine distributions? Moreover when were these creatinine

	levels determined vis-à-vis the timing of the bleed. **The admission serum creatinine was extracted from the electronic health records. We compared the serum creatinine levels in those who took each individual oral anticoagulant medication to those who took warfarin. There were no significant differences. Page 11, we have tried to make this statement clearer.** 14. Can the authors comment on comorbidities between OAC-bleed andon-OAC bleeds. It may be that warfarin users were "sicker" and at more risk for bleeding than new OAC **We did not extract data on comorbidities.**