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Title	Prescribing pattern of novel oral anticoagulants following regulatory approval for atrial fibrillation in ontario, Canada: a population-based descriptive study
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Reviewer 1	Colleen Maxwell PhD
Institution	Department of Pharmacy, University of Waterloo
General comments	This research letter addresses an important issue with regard to potential concerns regarding the apparent rapid uptake of novel medications among older frail patients who are typically not included in the clinical trials that form the basis for regulatory approval. As the analysis is restricted to aggregate monthly prescriptions (per 100,000 overall population), it is difficult to comment on, or clearly interpret the observed patterns without patient-specific data. Further, the comparison of the aggregate prescription data to the RE-LY trial appears fairly simplistic (it would be more interesting to understand the prescribing patterns for the oldest-old and to provide some comparisons of key demographic characteristics between those receiving the specific NOACs of interest with data provided by the relevant published trial(s). Some additional issues to address include: 1. It is unclear why overall population denominators were obtained from the Ontario Ministry of Finance (as opposed to the most recent Stats Canada figures)? Or are these the same figures? 2. With regard to age groups examined, it would be more informative to split up the 65-84 age group (to examine, minimally, those 65-74 and 75-84) as well as those 85+ as a separate group. 3. It would be interesting to provide age-specific estimates as well as age/sex-specific estimates, if possible. 4. Regarding lines 48-55, it is unclear why the authors have provided the overall volumes here for warfarin rather than estimates per 100,000 as done with the other agents. Also, the data presented in Figure 1 suggest continued high use of warfarin relative to the other agents - and this is not commented on (other than a note indicating that there seems to have been a slight reduction in prescriptions for warfarin, although the figure suggests somewhat stable use over time). 5. Regarding Figure 2, it would be helpful to provide comparable data for all of the agents of interest, not just dabigatran. 6. It would be informative for the authors to indicate, by age group and over time, the distribution of use for each of the agents of interest among those receiving any treatment.
Reviewer 2	Man-Chiu Poon XX
Institution	XXXXXXX
General comments	This interesting paper describes the prescribing habits of new oral anticoagulants (NOAC) since the approval of dabigatran and rivaroxaban by Health Canada. The paper aims to demonstrate the accelerated uptake of prescribing habits of NOACs in the "real world" and emphasizes the concerning trend of increasing NOAC prescriptions in high-risk bleeding populations, specifically the elderly. General Comments: This is a concise manuscript. The major strength is the simplicity of the study design in using prescription records from Canadian retail pharmacies in determining the monthly prescription volumes of all anticoagulants filled. This gives a broad and generalized account of the changing habits in prescribing patterns of Ontario physicians. The question is whether this prescription habit could be generalizable to the national community as a whole. In this respect, the authors should consider addition to their

	discussion the recent publication by Kirley et al (Circ Cardiovasc Qual Outcomes 2012; 5:615-621) showing the rapid adoption of NOAC (and dabigatran) for stroke prevention particularly in the elderly in the United States. The weaknesses generated by this design as addressed partially by the authors are: (1) The primary measured outcome is prescription volume rather than new prescription volume per patient. The authors also did an analysis restricted to new prescription and suggested this yielded similar trends – perhaps the analysis and data should be shown? (2) The inability to differentiate prescription indication (eg orthopaedic prophylaxis versus chronic AF resulting in potential overestimation of the true incidence of new prescription of NOACs for chronic AF. (3) Among the NOAC, the prescription pattern favors the use of dabigatran. For dabigatran there is a lack of information on dosage prescribed, particularly in the age >75 group, given that the overall bleeding risk with the lower dose (110 mg BID) in the elderly is lower than that with the higher dose (150 mg BID). This information is important to allow the readers to estimate the burden of bleeding in the elderly given the increasing prescription trend of this drug in this age group In this respect, it will be helpful to the general physician to provide a brief overview of the CCS recommendations for NOAC prescribing in elderly patients >75 years old. (4) There is no data on what proportion of NOAC prescriptions represent switching from warfarin therapy and on relative proportion of new diagnosis AF on warfarin vs NOAC therapy Other comments: Page 4, paragraph 3 (Results): what is the average age of the entire group of individuals prescribed a NOAC in the 24-month period that you looked at prescription trends. Page 5, paragraph 2, 2nd sentence. "…individuals aged 85 and above, a group in which RE-LY data suggest a more favorable bleeding risk profile with warfarin compared to dabigatran." The statement needs to be more specific given that in elderly individuals (age >=75), compared with warfarin use, intracranial bleeds are less when using dabigatran at either higher or lower dose, while extracranial bleeds (especially gastrointestinal bleeds) are higher with the higher dabigartran dose but similar with the lower dabigatran dose. I am unable to verify the statement from references 6 and 7. Furthermore, the RE-LY study cited in these two references did not provide analysis on patients aged >=85 as a discrete group. The authors should consider citing the subgroup safety results from the Eikelboom study published in Circulation (Circulation. 2011;123:2363-2372). Page 6, paragraph 1 (Interpretation): Would suggest including the average age (71 years old) of the study participants in the RE-LY study and that participants over the age of 85 were not analysis as a discrete group in this clinical trial. Grammar correction - Page 4, paragraph 2, second sentence: Furthermore, "the" percentage of …"
Author response	**REVIEWER 1** **Comment 1**: "The authors should consider addition to their discussion the recent publication by Kirley et al (Circ Cardiovasc Qual Outcomes 2012; 5:615-621) showing the rapid adoption of NOAC (and dabigatran) for stroke prevention particularly in the elderly in the United States." **Reply**: We have added Kirley et al's paper demonstrating similar uptake of dabigatran in the United States into our manuscript. However, as Kirley et al did not calculate the prescription rate of dabigatran in the elderly population, our data are still the first to demonstrate the remarkable rise in dabigatran prescription in the very elderly aged 85+. *Paragraph 1, Interpretation*: "The trend is consistent with data from the United States showing dabigatran rising as a proportion of oral anticoagulants, from 3.1% in the fourth quarter of 2010 to 18.9% one year later." **Comment 2**: The primary measured outcome is prescription volume rather than new prescription volume per patient. The authors also did an analysis restricted to new prescription and suggested this yielded similar trends – perhaps the analysis and data should be shown? **Reply**: In keeping with ensuring the concise nature of the manuscript and conforming with the limit placed on Research Letters (2 figures or tables), we were unable to include the figure demonstrating trends in new prescriptions in the manuscript resubmission. However, we have included this figure below and would be open for its

	inclusion in an Appendix at the editors' discretion. Restricting the analysis to new prescriptions of dabigatran, derived from the difference of total and refill prescription volumes, demonstrated similar trends (**Figure A**). While the new prescription rates overall appeared to plateau with time, the relative distribution of new dabigatran dispensing across age groups remained stable over time, with the highest rate amongst the very elderly aged 85 and above (**Figure B**). **Figure.** Age-stratified new prescription rates for dabigatran in Ontario among adults aged 20 and above, adjusted by population (A) and changes in proportion of new prescription rates by age group over time (B). **Comment 3**: The inability to differentiate prescription indication (eg orthopaedic prophylaxis versus chronic AF resulting in potential overestimation of the true incidence of new prescription of NOACs for chronic AF. **Reply**: This was addressed in the manuscript's limitations in the previous submission, as well as the current submission. We believe this limitation will not significantly impact our results, as per below: *Paragraph 3, Interpretation*: "While prescription volumes cannot be stratified by indications and include NOAC use in orthopedic surgery, its contribution to the overall prescription pattern is likely very limited: dabigatran and rivaroxaban have been approved for this indication since 2008, but prescriptions remained low until their approval for AF." **Comment 4**: Among the NOAC, the prescription pattern favors the use of dabigatran. For dabigatran there is a lack of information on dosage prescribed, particularly in the age >75 group, given that the overall bleeding risk with the lower dose (110 mg BID) in the elderly is lower than that with the higher dose (150 mg BID). This information is important to allow the readers to estimate the burden of bleeding in the elderly given the increasing prescription trend of this drug in this age group. In this respect, it will be helpful to the general physician to provide a brief overview of the CCS recommendations for NOAC prescribing in elderly patients >75 years old. **Reply**: We have included the dosage of dabigatran prescribed in the elderly population in this re-submission. In this edition, discussion re: CCS guidelines was removed, as we felt that it is more important to describe the overall trend and discuss its impact, irrespective of the reason why this trend occurred. Further, it is possible that growth of dabigatran in the very elderly is multi-factorial, influenced not only by CCS guidelines but other factors such as academic detailing, advertisement, etc. In its place, we have added in comparative safety data from CADTH and the FDA (ref. 13, 14), as below. *Paragraph 2, Results*: "By September 2012, 93.6% of dabigatran prescriptions amongst individuals aged ≥85 were for the 110mg dose." *Paragraph 2, Interpretation*: "In contrast to the RE-LY trial results for the 110 mg dose of dabigatran which suggested less major bleeding compared to warfarin,[14] a recent meta-analysis found comparable risks of major bleeding in patients ≥75 years.12 This corroborates a subgroup analysis of RE-LY participants ≥80 years submitted to the FDA by the trial sponsor." **Comment 5**: what is the average age of the entire group of individuals prescribed a NOAC in the 24-month period that you looked at prescription trends. **Reply**: Unfortunately, as the data were aggregates based on age groups, we are unable to provide the average age of the entire cohort, though it is likely higher given the higher percentage of patients >65 years in the Ontario cohort compared to RE-LY. However, this does not distract from main message of the paper, in that the highest growth in prescription rates of dabigatran was seen in the >85 age group. **Comment 6:** Page 5, paragraph 2, 2nd sentence. "…individuals aged 85 and above, a group in which RE-LY data suggest a more favorable bleeding risk profile with warfarin compared to dabigatran." The statement needs to be more specific given that in elderly individuals (age >=75), compared with warfarin use, intracranial bleeds are less when

	using dabigatran at either higher or lower dose, while extracranial bleeds (especially gastrointestinal bleeds) are higher with the higher dabigartran dose but similar with the lower dabigatran dose. I am unable to verify the statement from references 6 and 7. Furthermore, the RE-LY study cited in these two references did not provide analysis on patients aged >=85 as a discrete group. The authors should consider citing the subgroup safety results from the Eikelboom study published in Circulation (Circulation. 2011;123:2363-2372). **Reply**: According to results of the CADTH therapeutic review (ref. 13) and unpublished subgroup analysis submitted to the FDA (ref. 14), similar major bleeding risk with dabigatran 110mg compared to warfarin was reported in RE-LY participants over 75 years of age, in contrary to the overall trial results demonstrating favorable bleeding risks with lower-dose dabigatran. This is also consistent with the risk ratios of major bleeding risk reported in the Eikelmboom study. Of note, major bleeding risk by ISTH definition includes symptomatic bleeding into critical organs, one of which is intracranial bleeding. *Paragraph 2, Interpretation*: As per response to Comment 4. **Comment 7**: Page 6, paragraph 1 (Interpretation): Would suggest including the average age (71 years old) of the study participants in the RE-LY study and that participants over the age of 85 were not analysis as a discrete group in this clinical trial. **Reply**: This has been added in the current submission. An unpublished subgroup analysis was done for participants ≥ 85 years, which was also added. *Paragraph 2, Interpretation*: "Our results are the first to corroborate this perspective, demonstrating prescription rates of dabigatran to be most accelerated in the very elderly that is significantly older than the average trial participant (71 years)." **Comment 8**: Grammar correction - Page 4, paragraph 2, second sentence: Furthermore, "the" percentage of …" **Reply**: This has been added in the current submission. **REVIEWER 2** **Comment 1:** Further, the comparison of the aggregate prescription data to the RE-LY trial appears fairly simplistic (it would be more interesting to understand the prescribing patterns for the oldest-old and to provide some comparisons of key demographic characteristics between those receiving the specific NOACs of interest with data provided by the relevant published trial(s). **Reply:** We recognize that only age and dosage were evaluated in this study; however, we believe age is of particular interest given the higher bleeding risk in older patients combined with lack of an antidote. With respect to the "oldest-old", we have evaluated prescribing pattern for the very elderly (85+) and found an alarming increase in a group that showed different outcomes than the overall RE-LY trial results. **Comment 2:** It is unclear why overall population denominators were obtained from the Ontario Ministry of Finance (as opposed to the most recent Stats Canada figures)? Or are these the same figures? **Reply:** We have changed the denominator to the Stats Can figures with changes in outcomes. *Paragraph 2, Methods*: "Population data were based on the 2011 Canadian Census." **Comment 3:** With regard to age groups examined, it would be more informative to split up the 65-84 age group (to examine, minimally, those 65-74 and 75-84) as well as those 85+ as a separate group. It would be interesting to provide age-specific estimates as well as age/sex-specific

	estimates, if possible. **Reply:** We agree; however, the aggregate nature of the dataset did not allow us to separate it into finer resolution with respect to age/sex sub-groups. However, it does not take away from the manuscript's message re: the growth of dabigatran in the 85+ subgroup. **Comment 4:** Regarding lines 48-55, it is unclear why the authors have provided the overall volumes here for warfarin rather than estimates per 100,000 as done with the other agents. Also, the data presented in Figure 1 suggest continued high use of warfarin relative to the other agents - and this is not commented on (other than a note indicating that there seems to have been a slight reduction in prescriptions for warfarin, although the figure suggests somewhat stable use over time). **Reply:** We have amended the manuscript to incorporate warfarin prescriptions per 100,000. Warfarin use has declined somewhat, though it is more than offset by growth of NOACs. It suggests that oral anticoagulation overall has grown, for which there are a few reasons: 1. New recommendation that patients with CHADS = 1 should receive oral anticoagulant therapy, 2. Some newly diagnosed AF patients are receiving dabigatran without a prior trial of warfarin, in accordance to the Canadian Cardiovas. Society guidelines but contrary to the CADTH Common Drug Review recommendations. While important points, we felt that speculations on reasons of expanded oral anticoagulation was beyond the focus of this paper in an effort to keep the manuscript concise. *Paragraph 1, Results: "*Monthly prescriptions of warfarin over the study period decreased from 1,526 to 1,316 prescriptions per 100,000 individuals (p=0.007 for trend)." **Comment 5:** Regarding Figure 2, it would be helpful to provide comparable data for all of the agents of interest, not just dabigatran. It would be informative for the authors to indicate, by age group and over time, the distribution of use for each of the agents of interest among those receiving any treatment. **Reply:** With our goal of keeping the manuscript concise and within the 750-word limit of a Research Letter, we decided to focus on dabigatran as it was the agent with highest growth; rivaroxaban by study's end only made up 3.9% of the total oral anticoagulant prescriptions in Ontario.