Manuscript « Effectiveness and Safety of Direct Oral Anticoagulants versus Warfarin in Patients with Atrial Fibrillation and Chronic Kidney Disease »

In response to reviewer' comments: Many thanks for the excellent comments which improve the clarity of the manuscript. **We will find the modifications made based on reviews comments in yellow. The corrections for the cross check are in tracked changes.**

The affiliation of Dre Laurie-Anne Boivin-Proulx has been changed, as followed: **Laurie-Anne Boivin-Proulx**, Department of Cardiology, Faculty of Medicine, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)

Specific Comments to Authors: A reasonable effort was made in the study to address an important clinical question. However, the study has certain limitations which have been acknowledged by the authors. The INR and eGFR are two important factors which can lead to confounding bias in the study.
Response: We have already had addressed those limits at lines 332 to 334, as followed: Our study also had some limitations. Firstly, this observational study of administrative data might have been subject to confounding bias by unadjusted factors (e.g. the severity of AF, the exact eGFR, the international normalized ratio, body weight, over-the-counter prescriptions, and ethnicity).

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors:
1) The aim of this paper is fundamentally to provide data on safety and effectiveness of each individual DOAC, but only two molecules were considered. Thus, it should be clearer for readers a title such as "effectiveness and safety of apixaban and rivaroxaban versus warfarin in patients with atrial fibrillation and chronic kidney disease".
Response: We agree with the comment, and we have modified the title, as followed: Effectiveness and Safety of Aixaban and Rivaroxaban versus Warfarin in Patients with Atrial Fibrillation and Chronic Kidney Disease. We have had already mentioned the reasons why we were not able to assess dabigatran or edoxaban as shown at line 129-130 e.g. Few patients had a new prescription of either dabigatran or edoxaban and so were not included in our analysis. We also added a mention related to edoxaban and dabigatran in the legend of Figure 1, as followed: *No patients in the cohort received edoxaban, and patients using dabigatran were excluded for the low sample size between 2011-2017.

2) Stage III CKD was defined by a composite variable previously validated; however, the reference is restricted to a cohort comprised mostly older adults, and results may not be generalizable to all adults > 18 years as in the present studies;
Response: Many thanks for the comments, and this issue needs to be clarified. For instance, the mean age of the total cohort of atrial fibrillation patients published (e.g. Perreault S et al Pharmacotherapy 2019) and the mean age of atrial fibrillation patients with stage III CKD ranged from 69.9 to 86.2 and

from 79.1 to 82.9 years old, respectively. This is not surprising, giving the low prevalence of atrial fibrillation in younger population. Again, the mean age of the cohort used for the algorithm' validation of CKD stages (by Roy et al., 2020) ranged from 79.1 to 82.9 years old. Thus, we deleted 'age 18 and over' at the line 124, since this information is confusing. The line 124 was modified as followed: We identified adult patients with AF from January 1, 2013, to December 31, 2017.

3) Besides, and more importantly, the predictive algorithm was meant for identifying CKD GFR category 4-5, that is different from stage III considered in the present studies. These are very major limitations and should be adequately discussed.
Response: Many thanks for the comment which improves the clarity of the method used. In the manuscript of Roy et al 2020, we also reported the validity of CKD G3-5ND (using the algorithm 2), as followed: The validity of administrative data in determining the presence of CKD compared with the reference standard group CKD (G 3-5ND) is shown in Table S6. The algorithm 2 identifies CKD G3-5ND (as defined by a composite variable covering the ICD code and/or drug use) and led to sensitivity estimates ranging from 69;.2% to 72.1%, specificity ranging from 86.7% to 88.6%, PPV ranging from 90.5% to 91.5%. Thereafter, we used the algorithm 3 (as defined by a composite variable covering the ICD code, drug use, and consultations with a nephrologist) led to sensitivity estimates ranging from 82.5% to 89.0%, specificity ranging from 97.1% to 98.9%, PPV ranging from 94.5% to 97.7% to exclude patients with CKD G4-5ND in order to kept CKD G3ND. We thus modified the line 142-146, as followed: Lastly, the cohort was restricted to patients with stage III CKD by using the algorithm 2 to identify CKD G3-5ND, and then applying the exclusion of CKD G4-5ND by using the algorithm 3 (as defined by a composite variable covering the ICD code, drug use, and consultations with a nephrologist, as identified in the administrative databases). The composite variable has been validated, with reference to medical chart reviews of older adults with CKD (the algorithm used for estimated glomerular filtration rate (eGFR) definition presented a good positive predictives.[31]

4) It is not clear the reason of the use of the CHADS score instead of the CHADS2VASc score, now recommended in the atrial fibrillation guidelines. this point should be discussed, too. Anyway, it is useless to indicate CHADS constituents in a supplementary table, as they are well known.
Response: *First.* in Canadian clinical practice, CHADS2 is largely used. *Second*, our study period was from 2013 to 2018 (including the year of follow-up), and was aligned with the guideline of atrial fibrillation patients of the Canadian Cardiology Society (CCS). We have had the reference of CCS guideline at line 170.

Third, analysis using c-statistics showed that for patients with atrial fibrillation the CHADS2 and the CHA2DS2-VASc tools appear to perform similarly with respect to assessment of risk for stroke, thromboembolism or bleeding. Compared to the CHADS2, the CHA2DS2-VASc is better able to identify patients with very low risk of stroke or thromboembolism; And, it is well known that patients with CKD are high risk of stroke. *Four,* the Canadian Cardiology Society guideline recommended risk stratification using a predictive index for stroke and mentioned the CHAD65 algorithm. Moreover, in two guidelines (from USA and UK) the CHA2DS2-VASc score was recommended for assessing risk of stroke, and in two guidelines (from USA and Europe) it was not specifically mentioned that CHA2DS2-VASc score was recommended for assessing risk of stroke, however treatment recommendations were based on the CHA2DS2-VASc score.

Lastly, the Canadian Cardiology Society guideline recommended oral anticoagulant therapy for most atrial fibrillation patients of age ≥65 years or CHADS2 ≥1. Three guidelines recommended oral anticoagulant treatment for atrial fibrillation patients with CHA2DS2-VASc ≥2. One guideline

recommended oral anticoagulant therapy for male atrial fibrillation patients with CHA2DS2-VASc ≥2 and female atrial fibrillation patients with CHA2DS2-VASc ≥3. However, the evidence supporting the recommendations was not described in the guideline reports.

5) In the initial and final part of the discussion it is indicated that if creatinine clearance is 30-49 ml/min, there is the need to reduce the dose at 15 mg. This is a well-known general recommendation and should not be presented in that position, that should be reserved to the main study result. Reference 13 is related to a sub-analysis of the ARISTOTLE (not ARISTOLE) trial not focusing stage III CKD patients, so it is useless. In the study flow chart the patients excluded for taking dabigatran or edoxaban are not shown.
Response: First, we totally agree that the section related to *'but if creatinine clearance rate (CrCl) is between 30–49 mL/min, we need to reduce the dose at 15 mg'* at line 281 to 284 is not related to our results. We modified the sentence at line 281 to 282 as followed: Secondly, relative to warfarin, rivaroxaban appears to be effective and safe in AF patients with stage III CKD.

Second, reference 13 is related to a sub-analysis of the ARISTOTLE (not ARISTOLE) trial not focusing stage III CKD patients, so it is useless.
Response: Many thanks for the comment and we agree with the comment but, we modified the sentence related to *'A sub-analysis of the ARISTOTLE trial's data showed that apixaban reduced the rate of stroke and mortality relative to warfarin (regardless of the patient's level of renal function); however, the safety and effectiveness of apixaban vs. warfarin were not assessed specifically in stage III CKD patients'* by the new sentence at line 296 to 299, as followed: A sub-analysis of the ARISTOTLE trial's data showed that apixaban reduced the rate of stroke, mortality and major bleeding relative to warfarin among patients with impaired renal function (≤ 50 mL/min), when using creatinine-based estimates of GFR.

Third, in the study flow chart the patients excluded for taking dabigatran or edoxaban are not shown.
Response: We have added a mention related to edoxaban and dabigatran in the legend of Figure 1, as followed: *No patients in the cohort received edoxaban, and patients using dabigatran were excluded for the low sample size between 2011-2017. We have had already discussed this issue at line 129 to 130 as followed, Few patients had a new prescription of either dabigatran or edoxaban and so were not included in our analysis.

6) Minor suggestions figure 4) (; at page 12; page 15 "decline renal function"-> declined renal function or decline in renal function.
Response: It is done.

Reviewer anonymous

Reviewer Name:	**Anonymous**
Scientific Quality:	Grade B (Very good)
Novelty of This Manuscript:	Grade B (Good)
Creativity or Innovation of This Manuscript:	Grade B (Good)
Scientific Significance of the Conclusion in This Manuscript:	Grade B (Good)
Language Quality:	Grade B (Minor language polishing)

Specific Comments To Authors:

The aim of this paper is fundamentally to provide data on safety and effectiveness of each individual DOAC, but only two molecules were considered. Thus, it should be clearer for readers a title such as "effectiveness and safety of apixaban and rivaroxaban versus warfarin in patients with atrial fibrillation and chronic kidney disease".
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Response: See prior responses

These are very major limitations and should be adequately discussed. It is not clear the reason of the use of the CHADS score instead of the CHA2DS2VASc score, now recommended in the atrial fibrillation guidelines. this point should be discussed, too. Anyway, it is useless to indicate CHADS constituents in a supplementary table, as they are well known.
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