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Title	Cost-effectiveness of antithrombotic agents for atrial fibrillation in older adults at risk of falls
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Reviewer 1	Derek Chew
Institution	Department of Cardiac Sciences, University of Calgary, Calgary, Alta.
General comments (author response in bold)	Wong et al. present the findings of a cost-utility analysis exploring the value proposition of several strategie warfarin, and ASA) in older patients with non-valvular atrial fibrillation at high risk of falls. The authors addr patients with atrial fibrillation (i.e. the elderly) where there is an underutilization of appropriate OAC possibl falls and potential bleeding risk. The authors found that anticoagulation with apixaban was the most econo QALY gained compared to ASA. Main concerns: ASA as an anticoagulation strategy is problematic since as per the clinical guidelines referenced in the ma considered an anticoagulation. Rather, it is only used in the setting of AF patients at low stroke risk with co disease. In essence, the use of ASA is a "no anticoagulation" strategy with a bias towards increased bleed authors eliminate ASA as a strategy and only include DOACs / warfarin. **Although ASA is similar to "no anticoagulation," efficacy estimates from the literature point to stro lower bleeding risk compared with anticoagulants. In a geriatric population where bleeding risk is h the value of ASA as a treatment. Our results do not contradict the treatment guidelines. On the con over aspirin from an economic standpoint, which is not possible without including ASA. Also, anot bleeding risk options. On balance, we decided to keep ASA in the model.** To help visualize the different model inputs that result in variability of the estimated ICER, the authors shou deterministic sensitivity analysis. Specifically, is the model sensitive to falls as a clinical event? Under wha the value proposition of the different DOACs change? **We added deterministic sensitivity analyses for falls, age, and bleeding risk, as suggested. This is 146.** **"Deterministic sensitivity analyses were done on the effect of mean starting age, baseline probabil of first fall on average cost-effectiveness of each drug (Supplementary Figure SF4). Apixaban has h across the full range of falls risk and mean starting age. When baseline probability of clinically imp beyond 0.25 per year (model estimate 0.09), the model favoured ASA over apixaban."** The authors stated that variables that did not have variability (fixed costs) were inputted without distributio estimates were considered fixed (since there were no ranges specified). For generalizability of study findin the authors should consider modelling in the uncertainty / variability of drug pricing (e.g. drug costs +/- 50% for PSA) **Since this study is based in Ontario and the drug costs paid by the Ontario Drug Benefits program the prices fixed. It would be more helpful to run the model with specific costs for each province tha uncertainty in the model for fixed costs. We can do this if other provinces request the data.** Minor concerns: Abstract -- When stating that apixaban was economically favourable in 97% of microsimulations, the autho pay threshold used to benchmark cost-effectiveness (i.e., 50,000). **This has been added to the abstract.** **"There was moderate uncertainty in the ranking with apixaban as preferred choice in 66% of model to-pay of C$50,000/QALY)…" (Abstract document)**

	Extendedly dominated – While these terms are common place for the health economic literature, would su allow the manuscript to be more readily digested by the clinical audience. **We explain this in the Supplementary Appendix 1 in the Outcomes section. We also added a line to** **133).** **"When listed by increasing life-time cost, edoxaban, rivaroxaban and dabigatran were absolutely d** **dominated by extension by ASA and apixaban (Figure 1). Extended dominance means that the effe** **achieved with less cost by a combination of ASA and apixaban."** "ASA was the dominant strategy if the WTP threshold was below C$8,621" – would remove this sentence, of the manuscript. **This sentence was removed.**
Reviewer 2	Douglas Coyle
Institution	Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ont.
General comments (author response in bold)	When referencing the previous work relating to the cost effectiveness of DOACs it would be more relevant Canadian study that was funded through DSEN and CADTH than a non-Canadian study. **We substituted this citation in the introduction (page 1, lines 15-16).** **"The DOACs are economically attractive compared to warfarin in the general Canadian population** **an older population with falls is uncertain."** Under methods, the authors should begin with a concise description of the decision problem which their st **Due to space limitations, we have not repeated the decision problem in the methods. A concise des** **introduction.** I'm unconvinced about why the authors adopted a microsimulation approach to this study. It seems unnec more informative design would be to have divided the population into patient strata and conducted a stratif Strata could relate to the combination age, sex, HAS-BLED and CHADS scores. This would allow decision strata different treatments are optimal. **Two-dimensional microsimulations allow simulating individual patient characteristics similar to a r** **understanding the uncertainties around the overall best decision for a population, which is what a** **to know. Doing a stratified analysis is less efficient because multiple models would have to be run** **listed characteristics (age, sex, HAS-BLED, etc). We added deterministic sensitivity analysis to add** **conclusions with some of the characteristics listed here (age, bleeding risk, and falls risk).** Please change the term "within-cycle" to "half-cycle". **We changed the cited reference to highlight why "within-cycle" correction is more appropriate (pag** **preferred term in the current literature, which has changed since the ISPOR 2012 guidelines.** **"Within-cycle correction was used to compensate for biases occurring with discrete-time rather tha** **transitions [15]."** The explanation for the analysis under the Outcomes section is unclear. Were outcomes obtained from th by recent guidelines? Table 4 should be revised to present a sequential analysis – please follow the CADTH guidelines for this. **Yes, the outcomes were from a probabilistic analysis (two-dimensional microsimulation). Table 4 is** **follows CADTH guidelines (page 56 of CADTH guidelines:** **https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_tec** **We added additional outcomes explanation in supplementary appendix 1.** Under health states reference is made to a decision tree – is this correct? Earlier the model is described a more appropriate. Please also combine Figures 1 and 2 to represent a Markov model.

	The Markov model has health states where individuals encounter events. These events are indicate shown (supplementary figure SF1). The cycle diagram (supplementary figure SF2) shows the healt through. It's unclear whether the reviewer wants the two figures to be juxtaposed or if there's anot Please note that Figures 1 and 2 were put into the supplementary material to reduce number of figu There is much confusion over how the authors have incorporated variability which relates to heterogeneity which relates to the unknown true expected value. The authors sometimes seem to be confused with thes current model framework both variability (within the inner loop) and uncertainty (within the outer loop) need parameters. Currently, I feel they are greatly underestimating the uncertainty with their findings. **We elaborated more on uncertainty in the supplementary appendix. To our knowledge, it is not con parameter in both inner and outer loops. Our approach follows CADTH guidelines.** **"On an outer, second-order loop, parameter-level uncertainty was examined by selecting key mode representing the fact that estimates of parameter values derived from studies entail uncertainty. Fo sample, a set of inner loop iterations were run, each representing a hypothetical patient, whose cha risk (using CHADS score), bleeding risk (using HAS-BLED score), and falls risk—were sampled fro Sampling individual patient characteristics allows for both a representation of individual variability transition among various health states to depend on a given patient's attributes. We ran each hypo the anticoagulation strategies in turn." (Supplementary appendix 1).** For figure 3, please remove the term "average" from "average cost effectiveness plane". **We prefer including the term "average" because the plot indicates average cost-effectiveness valu reduce the number of figures and tables, we moved the first two figures to supplementary appendi** For figure 4, please change y-axis to "probability treatment is optimal". **This has been relabelled Figure 2. We kept "% iterations cost-effective" on the y-axis title because model iterations where the intervention is cost-effective. This can be interpreted as probability of t** For table 2, please provide the actual parameters used to populate the distributions – not a range which is insufficient data in Table 2 to determine the degree of variability and uncertainty in each data element. **This was included in the supplementary appendix in the original submission. See supplementary a** For table 4, it is unclear what the 95% confidence intervals relate to. Are they credible intervals which wou actual confidence intervals which are irrelevant as they are merely a function of the number of iterations. A the ICERs from each iteration or the difference in mean costs divided by the difference in mean QALYs? I **Yes, they should be called credible intervals. We have changed this in the revision for table 4.** For table 5, the same concern: it is unclear what the 95% confidence intervals relate to. Are they credible relevant or are they actual confidence intervals which are irrelevant as they are merely a function of the nu **Yes, we relabelled them credible intervals.**
Reviewer 3	Michael Hill, Dr. Hill, michael.hill@ucalgary.ca
Institution	Department of Clinical Neurosciences, University of Calgary, Calgary, Alta.
General comments (author response in bold)	1. This is a modelling study to attempt the differential utility of antithrombotic therapy strategies for patient This is a relevant clinical question that will not be likely to be studied with RCTs. Therefore, the modelling 2. Like all modelling studies, the outcome depends on the assumptions used, and how closely these mimi assumptions: A) In Canada reduced dosing regimens are available (eg. Apixaban 2.5mg bid, dabigatran 110 mg bid, riva particularly for elderly patients. These all have reduced efficacy, quantitatively, even if they cost the same disproportionately to the poopuation at risk of falling, who will typically be elderly. Please present data mo

We added 2 drug doses (dabigatran 110mg and edoxaban 30mg) and re-ran the entire model. Apixa
15mg do not have randomized data for efficacy estimates. In the randomized trial for apixaban, the
patients with 2 out of 3 characteristics for older age, low renal function or low body weight. There i
dose. Rivaroxaban 15mg dose is an off-label dose without formal efficacy estimates in randomized
This line was in the discussion in the original submission:
"Future studies can investigate whether low-dose (2.5mg) apixaban will reduce bleeding risk more
in this population [32]." (page 9, lines 199-201).

B) Patients states. Very often, if a patient is so disabled that they are bed bound, then it is not an option th
only will they be at reduced risk of falling, they would often not be anti coagulated. Please adjust model fo
We could not find guidelines indicating that patients who are bedbound should not be anticoagulat
would be a patient undergoing palliative care with limited life expectancy, but we did not simulate t

C) The distributions for model variables included in the simulation model are derived from 2 different cohor
fall risk and one cohort for CHADS and HAS BLED). Those two cohorts differ in their baseline characteristi
study vs. 70 in the AF-cohort). I believe this could potentially influence the model (as the calculated scores
baseline characteristics used in the model) and think that this should at least be mentioned in the limitation
This was added as a limitation in the discussion (page 9, lines 181-182).
"Fourth, the baseline individual characteristics was derived from two cohorts because no single co
sex, bleeding and stroke risk parameters."

3. Please provide a clear definition for bleeding events (major and minor)
Added (page 4 lines 86-89).
"Major bleeding is accompanied by a decrease in the hemoglobin level of at least 20 g/L or requirin
units of packed red blood cells, occurring at a critical site, or resulting in death [ref in body text]. M
bleed."

4. It is of major interest for the reader to see all the relevant comparisons. Please provide Figure S2 for ea
DOAC vs. warfarin. The focus on apixaban should be attenuated . If there are marginal differences betwe
basis of efficacy) it would be very helpful to know why the focus on apxiaban here is so prominent. (To this
was fully publicly funded and cannot be biased by industry funding).
We added a line in the discussion (page 9, lines 193-194) about the lack of industry influence in this
discussion because it was found to be most cost-effective, which is the main objective of the study
comparisons between the most cost-effective medication (apixaban) with drugs that were next mos
and edoxaban 30mg). Note that we added apixaban vs. edoxaban 30mg to this version supplement
found to be cost-effective in 31% of the model iterations.

5. Model validation: external validity of the simulation model was tested by comparing secondary outcome
Only cumulative number of falls and cumulative risk of stroke were used for comparison and validation. Wh
outcomes (life expectancy, cumulative bleeding, bedbound, time off medication)?
Life expectancy is based on life years, which is one of the outputs of the model, so it should not be
we don't validate QALYs or costs). We could not find suitable external cohorts for the other second
undertreatment of older adults with atrial fibrillation. One key assumption of the model is that all of
get treated with an antithrombotic agent. Clinicians often do not prescribe anticoagulants to older a
bleeding, which means population estimates of bleeding (and associated consequences) in this po
underestimated due to undertreatment. (See Clin Interv Aging. 2009;4:165, and Arch Intern Med. 20

6. We suggest being more cautious in the conclusions. This is a modelling study, and specifically not an o
is aimed at policy makers and physicians to help make predictive decision choices.
We changed the last sentence to:

	“The findings from this study can guide policies to encourage the use of economically attractive m **(page 9, lines 201-202)**