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Title	Screening for atrial fibrillation in canadian pharmacies: an economic evaluation
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General comments (author response in bold)	Tarride et al present an interesting study examining the cost-effectiveness of an outpatient atrial fibrillation (AF) screening program using a 30-second single lead ECG device in community pharmacies among individuals aged 65 years and older relative to no screening. The study is based on data from an actual intervention – the Program for the Identification of Actionable Atrial Fibrillation in the Pharmacy Setting (PIAFF) – involving 1,145 study participants. The investigators used a decision analysis model to estimate both short (based on direct intervention data above) and long-term (lifetime horizon; based on largely literature-derived estimates) costs as well as relevant patient outcomes associated with the strategy from a payer perspective. Several other studies in Australia, Sweden, and the Netherlands, for example, have shown favorable cost-effectiveness for such programs. While these studies limit the novelty of the current submission, this study provides Canadian estimates of cost-effectiveness. The findings of this study suggest the AF screening program is highly cost-effective with an estimated cost-effectiveness ratio of $375 per quality adjusted life year. A few comments for consideration are listed below: 1. The authors should be commended for applying a cost-effectiveness analysis on actual data from a community program for the short-term analysis – the availability of actual data that forms the basis of an economic evaluation is a strength of this study. **Thank you for the acknowledgment. No change in manuscript.** 2. A limitation, however, is the lack of data on a non-screened population. The authors assumed patients in the 'no screening' arm would remain undiagnosed for the remainder of the timeframe and would not receive OAC (page 5). This assumption may bias the findings in favour of the screening program and another study examining a similar AF screening strategy (Jacobs et al, Eurospace 2016) assumed approximately 3% of undiagnosed AF patients would be detected annually in routine practice. □ **We acknowledged this limitation in the Interpretation section and have further used a sensitivity analysis to estimate the impact of this assumption (Table 3 under proportion of undiagnosed AF individuals that become diagnosed each year).** □ **Our rationale to assume in the base case that everyone in the "no screening" arm would remain undiagnosed for the rest of their life is that currently there are no routine AF screening programs in pharmacies. The cost-effectiveness study by Jacobs et al (2016) was based on an AF screening program in GP offices during influenza vaccination. In that study, a single-lead ECG device was used to screen 3269 persons for AF during influenza vaccination sessions in 10 GP practices in the Netherlands (Kaasenbrood et al, Eurospace 2016). The screening identified 37 (1.1%) new AF cases. However Jacobs et al. (2016) assumed that 3% of undiagnosed AF patients will be detected annually in the GP office.** □ **To address this comment, we changed our base case analysis by assuming that 3% of undiagnosed AF would be diagnosed without screening. The underlined text below has been added to the Methods section under Model Structure. Deleted text is indicated by strikethrough.** ***"For the "no screening" arm, it is assumed that 3% of undiagnosed AF will be detected every year without screening.(New reference: Jacobs et al. Europace 2016) ~~For the "no screening" arm, individuals with undiagnosed AF are assumed to remain undiagnosed and therefore do not receive OAC therapy."~~*** 3. The authors estimate the total cost of screening by including costs related to training, in-pharmacy screening session costs, and costs of ECGs used within the screening program but don't seem to include costs of follow-up ECGs and Holter monitors. These costs may be relevant from a payer perspective. □ **The costs of follow-up ECGs and Holter monitors for those screening positive have been added to the calculations and in the text. Results were also updated. Overall this adds $1 to the cost per screened results and has almost no change in the results.** □ **To address this comment, the following underlined text has been added to the Methods section on Short-term Model Parameters.** ***"...and 3) costs of single-lead ECGs used within screening sessions and costs of confirmatory 12-lead ECGs and Holter monitors."*** □ **In addition, the tables in Appendix 1 and Appendix 2 have been modified to include these costs.** 4. The Swedish Atrial Fibrillation Cohort Study was used for estimates of stroke and major bleeding. This cohort study focused on patients diagnosed with AF in hospital, which may reflect a 'sicker' population than a simple community cohort who may largely be asymptomatic. It would be helpful to discuss the comparability of this cohort and the study population being assessed in the present cost-effectiveness analysis. □ **Thanks for identifying this additional limitation. We added this limitation in the text and briefly discussed the similarities and differences between the 2 cohorts.** □ **To address this comment, the following underlined text has been added in the 3rd paragraph of the Interpretation section.** **"There are a number of limitations to this economic evaluation. First, cost-effectiveness results were driven by predictions of ischemic stroke and other AF treatment events which were not observed but predicted based on short-term screening results. *For example, we used Swedish registry data for the estimates of stroke and major bleeding although the Swedish study focused on AF patients diagnosed in the hospital as opposed to our community-based cohort. More patients in the Swedish cohort reported a history of stroke, valvular diseases or heart failure. On the other hand the proportion of individuals with diabetes and hypertension was higher in our Canadian cohort. These differences (e.g. Swedish cohort may be sicker) should not impact our results as we applied the risk of stroke and ICH specific to the average CHADS2 score observed in our study. However we had to rely on the Swedish registry for the risk of major bleeding as the HAS-BLED scores were not collected in our study. "*** 5. On a note related to #4, the authors don't discuss the nature of the AF detected. How is 'actionable' defined – does the screening tool detect subclinical AF? More details in this regard would be helpful. □ **The screening was conducted using a single-lead ECG using a hand-held device (HeartCheck, CardioComm). As indicated in the text, the vast majority of our patients (96%) had unrecognized AF (e.g. sub-clinical AF). "Actionable AF" was defined as those with (i) previously unrecognized AF and (ii) known AF but not taking OAC medication.** □ **To address this comment we have added the following underlined text in the Introduction section.** ***"The Program for the Identification of 'Actionable' Atrial Fibrillation in the Pharmacy Setting (PIAAF-Pharmacy) was the first community AF screening program for individuals 65 years of older attending pharmacies in Alberta and Ontario using a handheld single lead ECG device (HeartCheck, CardioComm). "Actionable AF" was defined as those with (i) previously unrecognized AF and (ii) known AF but not***

taking OAC medication."

6. The authors assumed a roughly 50-50 split in treatment with warfarin and DOACs based on data that may be several years old. Are there data that reflect current trends in DOAC use (the utilization of DOACs relative to warfarin seems to be increasing over time) and would it be possible to project future use based on these trends? This may be important as DOACs are considerably more expensive than warfarin.

- To reflect this uncertainty, we initially conducted a sensitivity analysis where the DOAC had 100% market share (Table 3). The ICER increased to $8,611 per QALY gained.
- To address this comment, we reiterated in the third paragraph of the Interpretation section the sensitivity analyses that we conducted including the analysis assuming 100% market share for the DOACs.
  "To deal with the uncertainty associated with ~~some~~ key assumptions (e.g. cost per AF screen, proportion of AF receiving OAC, PPV, proportion of undiagnosed AF becoming diagnosed annually, OAC discontinuation rate, time horizon, stroke costs, assuming 100% use of DOAC and 0% use of warfarin) and associated parameter values, sensitivity analyses were conducted and indicated that the results were robust except for extreme and unlikely situations (Table 3)."

7. It was unclear how adherence to warfarin and DOACs was handled in this study.

- **Due to the limited available data, our base case model assumed 100% adherence with warfarin and DOACs. However, the cost-effectiveness study by Aaronson et al (2015) used a discontinuation rate based on the Aristotle study (Granger et al. N Engl J Med 2011). This study indicated that 25% of apixaban patients and 27% of warfarin patients had discontinued treatment after 30 months of treatment (or approximately 10% discontinuation per year).**
- **To address this comment, we changed our base case analysis to account for a discontinuation rate of 10% per year. Similar to Aaronson et al. (2015), additional sensitivity analysis using an annual discontinuation rate of 50% and 100% were conducted. The following text has been added to the Methods section under Short-term Model Parameters.**
  "Similar to the economic evaluation of Aaronson et al., a discontinuation rate to OACs of 10% per year was used in the base-case analysis scenario according to the ARISTOTLE trial (Granger et al. N Engl J Med 2011)."
- **In addition, the following underlined text has been added to the Methods section under Analysis of Uncertainty.**
  ***"In addition to the** PSA, deterministic sensitivity analyses were conducted in which cost-effectiveness results were evaluated while changing the value of a single model parameter at a time (cost per AF screen, proportion of AF receiving OAC, PPV, proportion of undiagnosed AF becoming diagnosed annually, time horizon, stroke costs, proportion of OAC that are DOACs, annual discontinuation to OACs)."*
- **Table 3, presenting the results of the sensitivity analyses, has also been updated to present these additional sensitivity analyses.**

8. The authors indicate in the methods section that a short-term as well as a long-term analysis was conducted and yet only the long-term analysis findings seem to be presented. It would be extremely helpful for the authors to present the short-term analysis as well.

- **Aligned with other economic evaluations of AF screening programs (Jacobs et al. 2016; Aaronson et al. 2015), the short-term analysis refers to the cost of screening and the outcomes of the screening. In this sense there are not really short-term results or long-term results. The short term model is used as input to the long-term model.**
- **To clarify this point, the following underlined text has been added to the Methods section under Study Overview.**
  "A decision analytical model was used to estimate the ~~short-term and long-term~~ lifetime costs and effects of the PIAAF-Pharmacy screening program compared to no screening. The model was comprised of two parts. The first part of the model captured the short-term costs (i.e. cost of screening) and outcomes (e.g. new cases of AF detected) of the screening program itself based on data from the PIAAF-Pharmacy study."
- **In addition, the following underlined text has been added to the Methods section under Model Structure.**
  "Figure 1a provides a graphical representation of the short-term decision model which describes the AF screening and is used as input for the long-term model"

9. The authors should re-check their reference listings (e.g. reference 13 does not reflect a Swedish cohort study).

- **Thank you for noticing this error. The citation for Friberg et al. (2012) has been corrected in the reference list.**

Other changes:

- **In addition to the changes outline above to answer the reviewers' comment, we changed the discount rate from 5% to 1.5% as per the 2017 "Guidelines for the Economic Evaluation of Health Technologies: Canada" (Canadian Agency for Drugs and Technologies in Health; 2017 March).**
- **Tables 1 and 3, Figure 2, and Appendices 1 and 2 have been updated to reflect the new base case scenario (i.e. 3% of undiagnosed AF will be detected every year without screening; inclusion of the cost of confirmatory 12-lead ECG ad Holter monitor; 10% discontinuation rates to OACs per year; 1.5% discount rate).**
- **In addition to the revisions indicated above, the following text was deleted from the Interpretation section in order to meet the word count guidelines for submission. This text provided further details on previous studies on AF screening and re-stated some of the information already presented in the Methods section under Short-term model parameters (i.e. proportion of screened individuals testing positive for AF, PPV).**
  ~~"This study assumed an underlying prevalence of undiagnosed AF of 1.4%, and a sensitivity and specificity of the AF screening test of 98.5% and 91.5%. The cost per screen was $AUD20 (CAN$20)."~~
  ~~"In this study the cost per screen was assumed to be €106 (CAN$ 156) and the percentage of screened individuals diagnosed with AF was assumed to be 3%. It was further assumed that 93% of patients identified with AF would receive an OAC. In comparison to these two studies, our model assumed in the base case analyses that 2.4% of seniors will test positive for AF for the first time at a cost of $65 per screened individual. Furthermore, we used a PPV of 65.4% to calculate the proportion of screened AF patients that are true positive (1.6%) and assumed that 71% of true positive patients will receive OAC treatment."~~
  ~~"Another limitation was related to the assumption around the percentage of individuals diagnosed with AF through screening that would end up being prescribed an OAC (71%). This percentage was based on~~

	~~*data from the PIAAF Pharmacy study in which 5 out of the 7 individuals who had seen their physician by six weeks were prescribed an OAC."*~~