

## Screening for atrial fibrillation in Canadian pharmacies: an economic evaluation

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### Abstract

**Background:** Screening for undiagnosed atrial fibrillation may lead to treatment with oral anticoagulation therapy, which can decrease the risk of ischemic stroke. The objective of this study was to conduct an economic evaluation of the Program for the Identification of 'Actionable' Atrial Fibrillation in the Pharmacy Setting (PIAAF–Pharmacy), which screened 1145 participants aged 65 years or more at 30 community pharmacies in Ontario and Alberta between October 2014 and April 2015.

**Methods:** We used a 2-part decision model to evaluate the short- and long-term costs and quality-adjusted life-years (QALYs) of a pharmacy screening program for atrial fibrillation compared to no screening. Data from the PIAAF–Pharmacy study were used for the short-term model, and the relevant literature was used to extrapolate the benefits of the PIAAF–Pharmacy study in the long-term model. Costs and QALYs were calculated from a payer perspective over a lifetime horizon and were discounted at 1.5%/year.

**Results:** Screening for atrial fibrillation in pharmacies was associated with higher costs (\$26) and more QALYs (0.0035) compared to no screening, yielding an incremental cost per QALY gained of \$7480. Univariate and probabilistic sensitivity analyses confirmed that screening for atrial fibrillation in a pharmacy setting was a cost-effective strategy.

**Interpretation:** Our results support screening for atrial fibrillation in Canadian pharmacies. Given this finding, efforts should be made by provincial governments and pharmacies to implement such programs in Canada. The addition of atrial fibrillation screening alongside screening and management of other cardiovascular conditions may help to reduce the burden of stroke.

Atrial fibrillation is the most common abnormal rhythm disorder<sup>1</sup> and the leading cause of stroke.<sup>2</sup> Although stroke related to atrial fibrillation is preventable with oral anticoagulation therapy,<sup>3,4</sup> the disorder is often unrecognized or is known but suboptimally treated (hereafter referred to as “actionable” atrial fibrillation).<sup>5</sup> There are sparse data to suggest that atrial fibrillation screening strategies are cost-effective.<sup>6,7</sup> In the Program for the Identification of 'Actionable' Atrial Fibrillation in the Pharmacy Setting (PIAAF–Pharmacy), which involved a pharmacist, a coordinator and volunteers in each pharmacy, people aged 65 years or more attending pharmacies in Alberta and Ontario were screened for atrial fibrillation with a hand-held single-lead electrocardiogram (ECG) device (HeartCheck, CardioComm Solutions).<sup>8</sup> The study design and clinical results were recently published.<sup>8</sup> Actionable atrial fibrillation in the PIAAF–Pharmacy study was defined as previously unrecognized atrial fibrillation or known atrial fibrillation that

was not being treated with oral anticoagulant therapy. The disorder was newly diagnosed in 2.4% of the 1145 study participants. The PIAAF–Pharmacy was modelled after the Cardiovascular Health Awareness Program.<sup>9,10</sup> The current analysis presents the economic evaluation of the PIAAF–Pharmacy study to better inform decision-makers about the value of screening for atrial fibrillation in Canadian pharmacies.

**Competing interests:** Jason Guertin received a Pfizer Canada Post-doctoral Mentoree Award outside the submitted work. Jeff Healey received research grants from Boehringer Ingelheim during the conduct of the study and grants from Bristol-Myers Squibb/Pfizer outside the submitted work. No other competing interests were declared.

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## Methods

We used a decision analytical model to estimate the lifetime costs and effects of the PIAAF–Pharmacy program compared with no screening. The model comprised 2 parts. The first part of the model captured the short-term costs (i.e., cost of screening) and outcomes (e.g., new cases of atrial fibrillation detected) of the screening program itself based on data from the PIAAF–Pharmacy study.<sup>8</sup> The second part of the model captured the long-term costs and benefits associated with stroke prevention resulting from the diagnosis of previously unrecognized atrial fibrillation based on relevant literature. In the absence of dominance (e.g., 1 strategy is more effective and less costly than the other), we calculated an incremental cost per quality-adjusted life-years (QALYs) gained to compare the 2 strategies (in-pharmacy atrial fibrillation screening v. no screening). We used a lifetime horizon in the analysis, with costs and outcomes occurring in the future discounted at an annual rate of 1.5%.<sup>11</sup> The analysis was taken from a third-party public payer perspective. We conducted univariate and probabilistic sensitivity analyses to deal with uncertainty in model inputs.

## Model structure

Figure 1, A, provides a graphical representation of the short-term decision model for atrial fibrillation screening, which is used as input for the long-term model. In the screening arm, atrial fibrillation is diagnosed based on positive findings of the single-lead ECG and its positive predictive value (PPV) to identify atrial fibrillation. A proportion of people with newly diagnosed atrial fibrillation would receive oral anticoagulant treatment for the prevention of stroke. For the no-screening arm, it is assumed that 3% of cases of undiagnosed atrial fibrillation would be detected every year without screening.<sup>12</sup> Based on the short-term decision tree, people enter the long-term model (Figure 1, B) in 1 of 3 health states: 1) no atrial fibrillation, 2) atrial fibrillation being treated with oral anticoagulant therapy or 3) atrial fibrillation not being treated oral anticoagulant therapy. Those with atrial fibrillation are at risk for ischemic stroke, intracranial hemorrhage and nonintracranial major bleeding. Intracranial hemorrhage is further divided into hemorrhagic stroke and nonhemorrhagic stroke. People with atrial fibrillation who are receiving oral anticoagulant therapy are assumed to be at lower risk for ischemic stroke but at higher risk for intracranial hemorrhage and nonintracranial major bleeding compared to those not receiving oral anticoagulant therapy. Transitions between health states can occur every 3 months.

## Short-term model parameters

Based on the PIAAF–Pharmacy study results,<sup>8</sup> we assumed that 2.4% of those in the screening group would have a positive result for atrial fibrillation for the first time. The PPV of the single-lead ECG used in that study, 65.4%, was based on unpublished data from a similar atrial fibrillation screening study conducted in physicians' offices (as opposed to pharmacies) in which all those with a positive result of single-lead ECG underwent 12-lead ECG and, if that gave a negative result, Holter monitor testing (Dr. Russell Quinn, Libin Cardiovascu-

lar Institute of Alberta, University of Calgary, Calgary, Alta.: personal communication, 2016). We applied the PPV to this percentage to calculate the proportion of screened people who have newly diagnosed atrial fibrillation ( $2.4\% \times 65.4\% = 1.6\%$ ). We assumed that 71% of people with newly diagnosed atrial fibrillation would receive oral anticoagulant treatment for the prevention of stroke based on the fact that 5 of the 7 participants in the PIAAF–Pharmacy study in whom atrial fibrillation was newly diagnosed saw a physician within 6 weeks after screening and were prescribed oral anticoagulant therapy by the end of the 3-month study follow-up period. As in the economic evaluation of Aronsson and colleagues,<sup>6</sup> we used a rate of discontinuation of oral anticoagulant therapy of 10% per year in the base-case analysis scenario according to the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.<sup>13</sup> We used cost data from the PIAAF–Pharmacy study to calculate the cost per screen by dividing the total cost of the screening sessions conducted in the study by the number of participants screened in the study. We estimated the total cost of the screening sessions by summing 3 cost categories: 1) training of personnel conducting the screening sessions, 2) in-pharmacy screening sessions, including transmission of results to family physicians, and 3) costs of single-lead ECG used in screening sessions and of confirmatory 12-lead ECG and Holter monitor testing.<sup>14</sup>

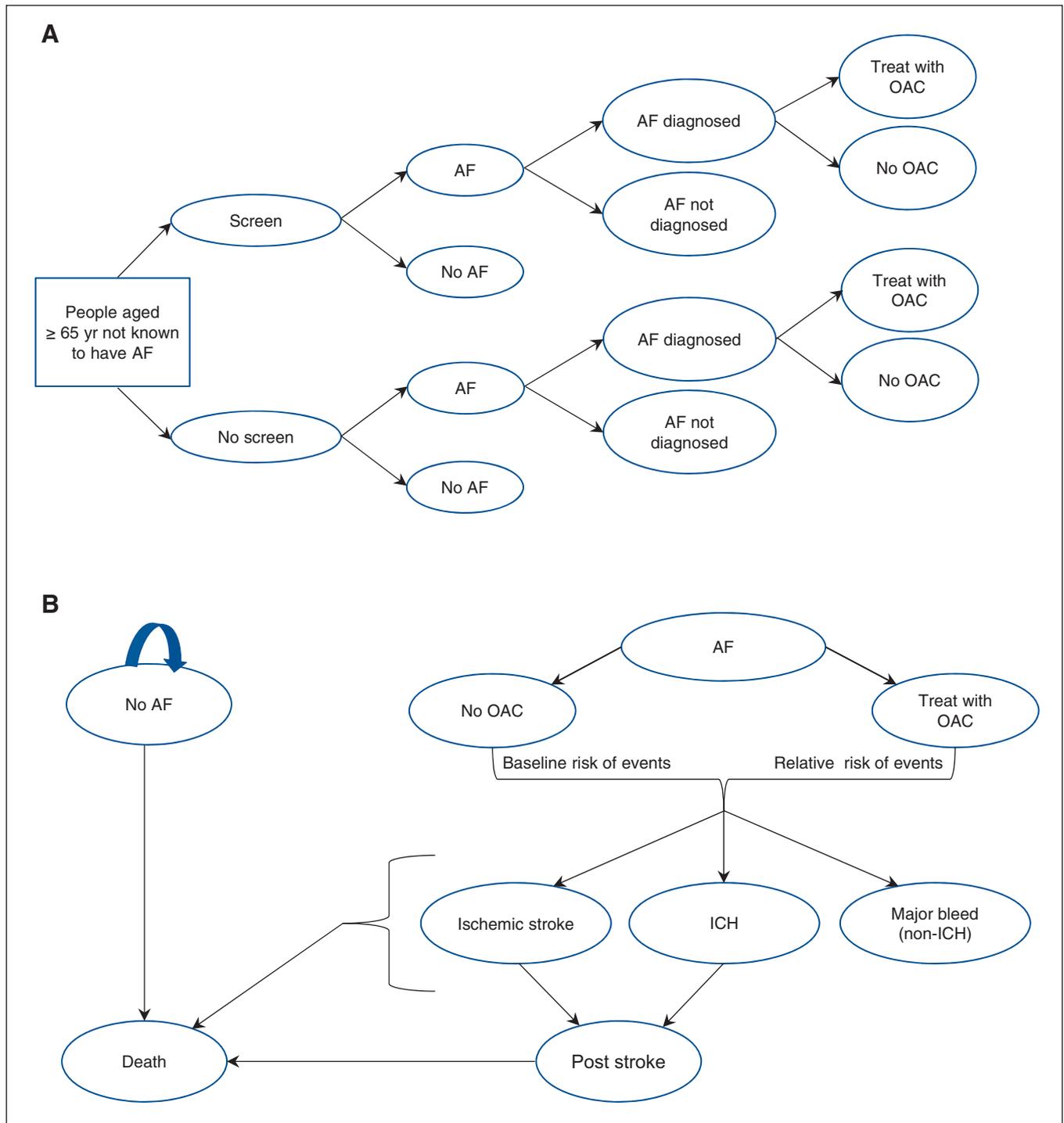
## Long-term model assumptions

The key assumptions for the long-term model regarding stroke and bleeding risk, mortality, cost of events and utilities are presented in the following sections. A summary of the long-term model variables is also provided in Appendix 1 (available at [www.cmajopen.ca/content/5/3/E653/suppl/DC1](http://www.cmajopen.ca/content/5/3/E653/suppl/DC1)) along with other model inputs used in the short- and long-term models (e.g., cost and utility data).

## Stroke and bleeding risk

We used the average CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>15</sup> for participants with newly diagnosed atrial fibrillation in the PIAAF–Pharmacy study, 3.3, in the model. The annual risk of stroke in the absence of oral anticoagulant therapy and the risk of intracranial hemorrhage and nonintracranial major bleeding for people with atrial fibrillation were based on findings from a Swedish cohort study involving 182 000 people in whom atrial fibrillation was diagnosed.<sup>16</sup> We also used the average HAS-BLED score<sup>17</sup> in that study, 2.18, for our model cohort because these scores were not captured in the PIAAF–Pharmacy study.

For people with atrial fibrillation who receive oral anticoagulant therapy, we applied the relative risk of ischemic stroke and major bleeding compared to those not receiving oral anticoagulant therapy separately for those treated with warfarin and for those treated with direct oral anticoagulant therapy. For people treated with warfarin, the relative risk of ischemic stroke and major bleeding was based on a meta-analysis by Lip and Edwards.<sup>18</sup> For those who received direct oral anticoagulant therapy, we used data from a meta-analysis of ischemic stroke and major bleeding relative to warfarin.<sup>4</sup>



**Figure 1:** Graphical representation of short-term (A) and long-term (B) atrial fibrillation (AF) screening model. People enter the long-term model in 1 of 3 health states: 1) no AF, 2) AF being treated with oral anticoagulant (OAC) therapy or 3) AF not being treated with OAC therapy. The curved blue arrow indicates that people with no AF are assumed to remain with no AF for the remainder of the model or until death. Note: ICH = intracranial hemorrhage.

We estimated the relative risk of events associated with direct oral anticoagulant therapy compared to no treatment indirectly by multiplying the relative risk of events for direct oral anticoagulant therapy versus warfarin by the relative risk of events for warfarin compared to no treatment.

#### Mortality

For people without atrial fibrillation and for those with atrial fibrillation who do not experience an event (e.g., stroke), we applied age- and sex-specific mortality rates based on Canadian life tables.<sup>19,20</sup> The 1-year mortality rate after ischemic

stroke, 37.3%, was based on findings from McGrath and colleagues.<sup>21</sup> The 1-year mortality rate following intracranial hemorrhage, 35.2%, was based on in-hospital mortality reported by Alonso and colleagues<sup>22</sup> extrapolated to 1-year mortality following intracranial hemorrhage by applying the ratio of 30-day mortality to 1 year, as observed for ischemic stroke by McGrath and colleagues.<sup>21</sup> We assumed mortality rates 1 year following stroke (ischemic or hemorrhagic) to be 2.3 times higher than for the general population based on data from Hardie and colleagues.<sup>23</sup> Nonintracranial major bleeding was associated with a mortality rate of 7.4%.<sup>24</sup>

### Cost of events

Based on Canadian registry data, we assumed that 52% of people receiving oral anticoagulants would receive warfarin and 48% would receive direct oral anticoagulant therapy.<sup>25</sup> The cost of warfarin was based on a regimen of 5 mg per day. We also assigned monitoring costs to those receiving warfarin based on estimates used in a Canadian economic evaluation of atrial fibrillation treatments.<sup>26</sup> Unit costs of orally administered anticoagulants were based on 2016 reimbursement prices from the Ontario Drug Benefit formulary.<sup>27</sup> For people who had an ischemic stroke or an intracranial hemorrhage, we assigned separate costs for the first year and for subsequent years following the event based on Canadian data.<sup>28–31</sup> All costs are expressed in 2016 Canadian dollars. When necessary, we used the health care component of the Canadian Consumer Price Index to adjust to 2016 Canadian dollars.<sup>32</sup>

### Utilities

We assigned age- and sex-specific general population EQ-5D utility values to people (with or without atrial fibrillation) with no events.<sup>33</sup> EQ-5D is a preference-based measure of health status that is widely used in clinical trials, observational studies and other health surveys. People with an ischemic stroke or intracranial hemorrhage (hemorrhagic or nonhemorrhagic stroke) were assigned a utility weight of 0.60 to reflect the decreased long-term quality of life after these events. We estimated this utility weight by combining the average utility for stroke according to the score on the modified Rankin Scale (a commonly used scale for measuring the degree of disability or dependence in activities of daily living of people who have had a stroke) (mRS 0–2, mRS 3–5)<sup>34</sup> with the proportion of people in these modified Rankin Scale categories, as derived from

data from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) trial.<sup>35</sup> We multiplied the stroke utility weight by the age- and sex-specific population utility value for the cohort of patients who have a stroke.

### Analysis of uncertainty

We first evaluated the uncertainty around the base-case cost-effectiveness results using probabilistic sensitivity analyses,<sup>36</sup> in which we simulated the model results 1000 times, with values from model input variables being drawn from distributions specific to each model parameter (Appendix 1) by means of Monte Carlo techniques. We expressed parameter uncertainty around the base-case results using a cost-effectiveness acceptability curve, which shows the probability that atrial fibrillation screening is cost-effective across different willingness-to-pay thresholds.

In addition, we conducted deterministic sensitivity analyses in which we evaluated cost-effectiveness results while changing the value of a single model parameter at a time (cost per atrial fibrillation screen, proportion of people with atrial fibrillation receiving oral anticoagulant therapy, PPV, proportion of cases of undiagnosed atrial fibrillation that are diagnosed annually, time horizon, costs associated with stroke, proportion of orally administered anticoagulants that are direct and annual rate of discontinuation of oral anticoagulant therapy).

### Ethics approval

The PIAAF–Pharmacy study was approved by the Human Research Ethics Board at the University of Alberta and the Hamilton Integrated Research Ethics Board.

### Results

With a cost per person screened of \$66 (Appendix 2, available at [www.cmajopen.ca/content/5/3/E653/suppl/DC1](http://www.cmajopen.ca/content/5/3/E653/suppl/DC1)), the model estimated that, compared to no screening, the PIAAF–Pharmacy screening intervention would result in higher expected costs (\$26), more life-years (0.0032) and more QALYs (0.0035) over a lifelong time horizon, yielding an incremental cost per QALY gained of \$7480 (Table 1). The increased per-person costs associated with the screening strategy (\$66) and oral anticoagulant management (\$29) are partially offset by the decreased costs associated with ischemic stroke (–\$90) (Table 2).

Intervention	Cost, \$	No. of life-years	No. of QALYs	Incremental \$/ life-year gained	Incremental \$/ QALY gained
PIAAF–Pharmacy screening	443.99	9.027	6.880		
No screening	417.93	9.023	6.876		
Incremental	26.06	0.0032	0.0035	8213	7480

Note: PIAAF–Pharmacy = Program for the Identification of 'Actionable' Atrial Fibrillation in the Pharmacy Setting, QALY = quality-adjusted life-year.

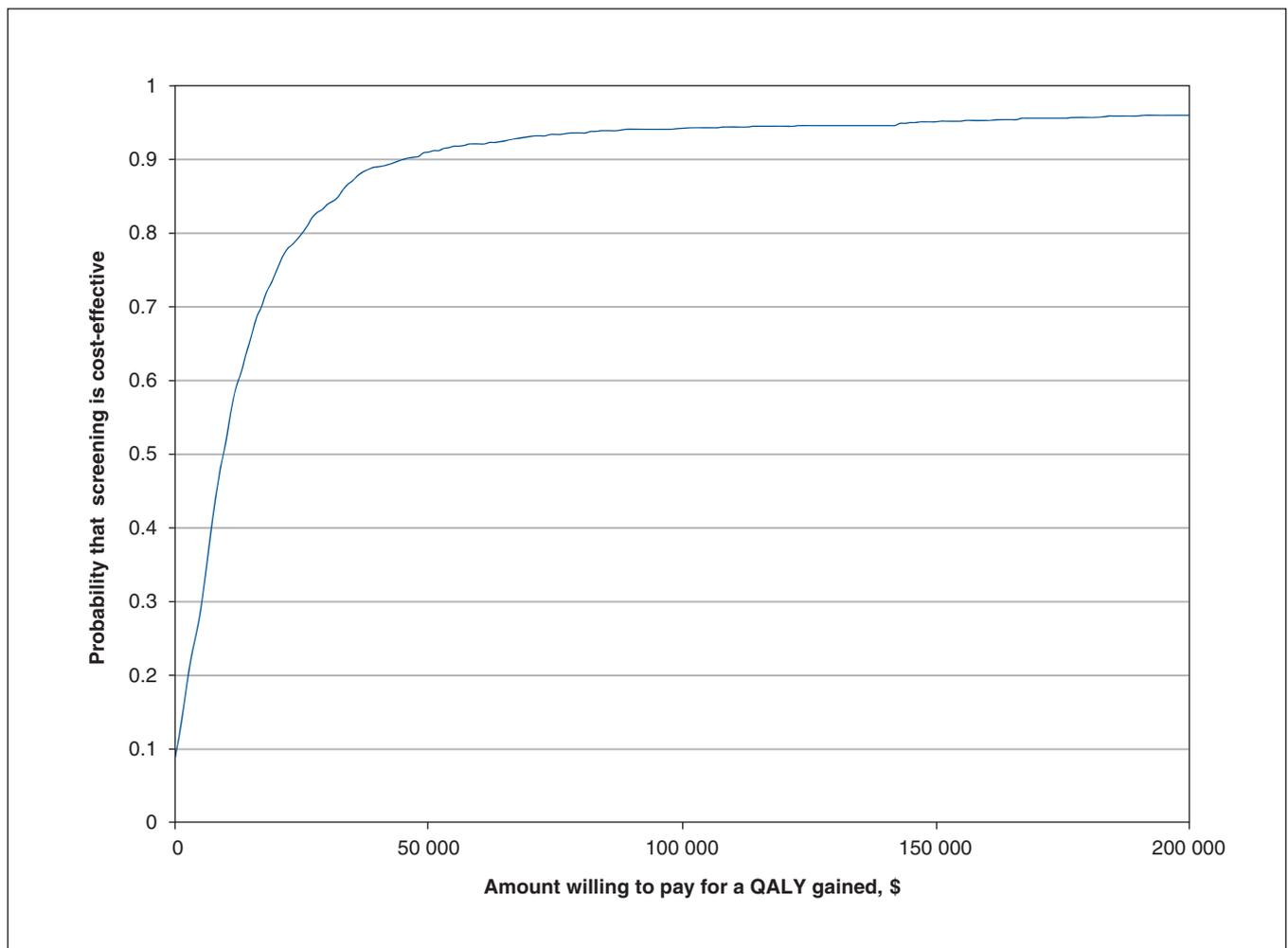
Probabilistic sensitivity analyses indicated that the probability that atrial fibrillation screening is cost-effective is 91% and 94% if the willingness to pay for a QALY gained is \$50 000 and \$100 000, respectively (Figure 2). The atrial fibrillation screening strategy is dominant or costs less than \$50 000 per QALY in all deterministic sensitivity analyses except where 1) the proportion of people with confirmed

atrial fibrillation who receive oral anticoagulant therapy is 20% or less (compared to 71% in the base-case analysis), 2) the PPV of single-lead ECG is 0.20 or lower (compared to 0.654 in the base-case analysis) or 3) the annual proportion of people with atrial fibrillation in the no-screening arm in whom the disorder is diagnosed symptomatically is 50% or higher (compared to 3% in the base-case analysis) (Table 3).

**Table 2: Expected costs by category**

Intervention	Category; cost, \$					Total
	Intervention	Oral anticoagulant therapy	Ischemic stroke	Intracranial hemorrhage	Major bleeding	
PIAAF–Pharmacy screening	66	35	269	55	20	443.98
No screening	0	5	358	41	13	417.93
Incremental	66	29	–90	13	7	26.06

Note: PIAAF–Pharmacy = Program for the Identification of 'Actionable' Atrial Fibrillation in the Pharmacy Setting.



**Figure 2:** Cost-effectiveness acceptability curve.

**Table 3 (part 1 of 2): One-way sensitivity analyses, PIAAF–Pharmacy screening versus no screening (base case: incremental cost per QALY gained = \$1175)**

Variable	Incremental cost, \$	Incremental no. of QALYs	Incremental cost/QALY gained, \$
Cost of screening, \$ (base case = \$65)			
100	60	0.0035	17 195
90	50	0.0035	14 325
80	40	0.0035	11 455
70	30	0.0035	8585
60	20	0.0035	5715
50	10	0.0035	2845
40	–0	0.0035	Dominates
30	–10	0.0035	Dominates
% of people with newly diagnosed atrial fibrillation who receive oral anticoagulant therapy (base case = 0.71)			
1.0	10	0.0049	2056
0.9	16	0.0044	3562
0.8	21	0.0039	5446
0.7	27	0.0034	7867
0.6	32	0.0029	11 096
0.5	38	0.0024	15 616
0.4	44	0.0020	22 397
0.3	49	0.0015	33 697
0.2	55	0.0010	56 298
0.1	61	0.0005	124 101
Positive predictive value of single-lead electrocardiography (base case = 0.654)			
1.0	5	0.0053	911
0.9	11	0.0048	2291
0.8	17	0.0043	4015
0.7	23	0.0037	6232
0.6	29	0.0032	9189
0.5	36	0.0027	13 327
0.4	42	0.0021	19 535
0.3	48	0.0016	29 882
0.2	54	0.0011	50 575
0.1	60	0.0005	112 656

## Interpretation

The main findings of this economic evaluation of the PIAAF–Pharmacy study indicate that screening people aged 65 years or more for atrial fibrillation in Canadian pharmacies is highly cost-effective compared to no screening, yielding an incremental cost/QALY gained of \$7480. The upfront costs associated with screening are partially offset by reductions in costs

related to ischemic stroke owing to the initiation of oral anti-coagulant treatment after atrial fibrillation is diagnosed. Except in unlikely situations (e.g., 20% of people with newly diagnosed atrial fibrillation would be prescribed oral anticoagulant therapy), the screening strategy was the dominant or a cost-effective strategy in all sensitivity analyses, which improves our confidence in the results. These results can be explained by the high costs associated with ischemic stroke

**Table 3 (part 2 of 2): One-way sensitivity analyses, PIAAF–Pharmacy screening versus no screening (base case: incremental cost per QALY gained = \$1175)**

Variable	Incremental cost, \$	Incremental no. of QALYs	Incremental cost/QALY gained, \$
% of people with undiagnosed atrial fibrillation in whom the disorder is diagnosed each year (base case = 0.03)			
0	20	0.0040	4951
0.05	30	0.0032	9215
0.1	36	0.0027	13 724
0.2	45	0.0019	23 499
0.3	50	0.0015	34 355
0.4	53	0.0011	46 475
0.5	56	0.0009	60 186
Time horizon, yr (base case = lifetime)			
5	36	0.0010	37 226
10	25	0.0023	10 657
15	25	0.0031	7800
20	26	0.0034	7490
25	26	0.0035	7480
Annual rate of discontinuation of oral anticoagulant therapy (base case = 10%)			
0	1	0.005	232
0.1	26	0.003	7480
0.2	38	0.002	15 480
0.3	45	0.002	24 333
0.4	50	0.001	34 208
0.5	53	0.001	45 382
Alternative stroke costs	46	0.003	13 277
Warfarin represents 100% of orally administered anticoagulants*	17	0.003	5985
Direct oral anticoagulant therapy represents 100% of orally administered anticoagulants†	36	0.004	8611
Note: PIAAF–Pharmacy = Program for the Identification of ‘Actionable’ Atrial Fibrillation in the Pharmacy Setting, QALY = quality-adjusted life-year. *Base case: 52%. †Base case: 48%.			

and the associated value in preventing stroke comparing to the cost of screening and managing newly diagnosed cases of atrial fibrillation.

Our findings are fairly consistent with those of a cost-effectiveness analysis of an Australian in-pharmacy atrial fibrillation screening program among people aged 65 years or more, which yielded an incremental cost per QALY gained of A\$5988 (Can\$5928<sup>37</sup>).<sup>7</sup> In Sweden, the long-term cost-effectiveness of a nonpharmacy mass atrial fibrillation screen-

ing program was estimated to be €4313/QALY gained (Can\$6341<sup>37</sup>),<sup>6</sup> and a similar study conducted in the Netherlands showed screening in primary care to be the dominant strategy.<sup>12</sup>

### Limitations

In this economic evaluation, cost-effectiveness results were driven by predictions of ischemic stroke and other events related to atrial fibrillation or oral anticoagulant treatment

that were not observed but were predicted based on short-term screening results. For example, in the absence of Canadian data, we used Swedish registry data<sup>16</sup> for the estimates of stroke and major bleeding, although the Swedish study focused on atrial fibrillation diagnosed in the hospital as opposed to our community-based cohort. More patients in the Swedish cohort than in our cohort reported a history of stroke, valvular disease or heart failure. On the other hand, the proportions of people with diabetes and hypertension were higher in our cohort. These differences (e.g., the Swedish cohort may have been sicker) should not have affected our results, as we applied the risk of stroke and intracranial hemorrhage specific to the average CHADS<sub>2</sub> score observed in our study. However, we had to rely on the Swedish registry data for the risk of major bleeding, because HAS-BLED scores were not collected in our study. In addition, the PIAAF-Pharmacy screening program is less likely to identify cases of intermittent atrial fibrillation than persistent or permanent atrial fibrillation. To deal with the uncertainty associated with key assumptions (e.g., cost per screen, proportion of people with atrial fibrillation receiving oral anticoagulant therapy, PPV) and associated parameter values, we conducted sensitivity analyses, which indicated that the results were robust except for extreme and unlikely situations. Our economic evaluation focused only on atrial fibrillation, and we did not integrate additional benefits associated with the PIAAF-Pharmacy study, such as the detection of other modifiable stroke risk factors (e.g., high blood pressure or risk of diabetes), which have already been shown to be clinically and economically advantageous.<sup>9,10</sup> Inclusion of those additional factors would result in additional benefits associated with the program and would most likely result in overall cost-savings. As per the study design, the intervention was conducted by study coordinators and volunteers during scheduled screening sessions. As a result, some of their time in the pharmacy was spent waiting for eligible participants. It is reasonable to consider that an atrial fibrillation screening program could be better integrated into pharmacy workflows in collaboration with other pharmacy programs such as vaccinations, which would reduce waiting time and therefore the cost per person screened. Nonetheless, pharmacists will need to show adequate training in atrial fibrillation screening and sufficient resources and remuneration to perform this new service. Collaboration with physicians will also be key to ensure proper follow-up.

## Conclusion

The results of this study have several policy implications. The PIAAF-Pharmacy study indicated that screening for atrial fibrillation and other modifiable risk factors in the pharmacy setting is feasible and is the dominant or cost-effective strategy compared to no screening, even at a cost of \$66 per screen. Given this, efforts should be made by provincial governments and pharmacies to implement such programs in Canada. Adding atrial fibrillation screening in pharmacies should be considered along with other evidence-informed screening for cardiovascular disorders to identify

those at high risk. Future research should focus on generating Canadian risk equations for stroke and major bleeding events.

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