Cost-effectiveness of atrial fibrillation screening in Canadian community practice

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BACKGROUND Contemporary guidelines recommend opportunistic screening for atrial fibrillation (AF).

OBJECTIVE The objective of this study was to assess the cost-effectiveness of single time point opportunistic AF screening for patients 65 years and older by using the single-lead electrocardiogram.

METHODS An established Markov cohort model was adapted by updating the background mortality estimates, epidemiology, screening efficacy, treatment patterns, resource use, and cost inputs to reflect a Canadian health care setting. Inputs were derived from a contemporary prospective screening study performed in Canadian primary care settings (screening efficacy and epidemiology) and the published literature (unit costs, epidemiology, mortality, utility, and treatment efficacy). The impact of screening and oral anticoagulant treatment on the cost and clinical outcomes was analyzed. A Canadian payer perspective over lifetime was used for analysis, with costs expressed in 2019 Canadian dollars.

RESULTS Among the estimated screening-eligible population of 2,929,301 patients, the screening cohort identified an additional 127,670 AF cases compared with the usual care cohort. The model estimated avoidance of 12,236 strokes and incremental quality-adjusted life-years of 59,577 (0.02 per patient) over lifetime in the screening cohort. Cost savings were substantial because of improved health outcomes, reflecting screening being the dominant strategy (affordable and effective). Model results were robust across sensitivity and scenario analyses.

CONCLUSION Single time point opportunistic screening of AF using a single-lead electrocardiogram device in Canadian patients 65 years and older without known AF may provide improved health outcomes with cost savings from the perspective of a single payer health care environment.

KEYWORDS Atrial fibrillation; Screening; Cost-effectiveness; Stroke; Bleeding; Anticoagulation

(Heart Rhythm O^2 2023;4:103–110)

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac dysrhythmia encountered in clinical practice, affecting ~2%–3% of the general population.[1] In addition to reductions in quality of life, AF accounts for the majority of arrhythmia-related health care encounters and is associated with a 4-fold increased risk of premature mortality and a 5-fold increased risk of thromboembolism.[1] Moreover, AF-associated strokes are more severe than other stroke etiologies, being associated with greater long-term disability and a significantly higher mortality when compared with non-AF strokes.[2–4] Oral anticoagulation (OAC) therapy reduces the incidence of stroke by more than two-thirds and has been shown to improve survival in the population with AF.[5]

Recognizing that a significant proportion of patients with undiagnosed AF may be asymptomatic and that stroke is the first clinical manifestation of undiagnosed AF in up to 20% of patients, it has been postulated that systematic screening may provide an opportunity for early identification of patients with AF who would benefit from stroke prevention therapies.[6–9] However, while recent community-based studies have demonstrated that screening is effective at diagnosing new cases of AF,[9] it is important to consider the cost-effectiveness of such an approach before implementing routine AF screening into practice. The aim of the present study was to assess the cost-effectiveness of opportunistic

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2666-5018/

https://doi.org/10.1016/j.hroo.2022.11.003

KEY FINDINGS

- A significant number of at-risk patients have undetected atrial fibrillation.
- Opportunistic screening can help identify patients at risk of adverse outcomes related to atrial fibrillation.
- Compared with usual care, opportunistic screening results in a significant decrease in downstream adverse health outcomes and future health expenditures.

single-lead electrocardiographic (ECG) screening in patients 65 years and older by using a health economic model.

Methods

An economic evaluation of AF screening must consider (1) the screening participation rate, (2) the proportion of undiagnosed AF in the (target) population, (3) the difference in the rate of AF detection between the screening population and those receiving usual care, (4) the risk of adverse clinical outcomes in the target population (eg, stroke risk), (5) the risk and benefit associated with intervention (eg, OAC-enabled stroke risk reduction and the increase in bleeding), and (6) the acceptable threshold for willingness to pay.[10]

Model structure

An established and validated Markov cohort model[11] was employed (Online Supplemental Figure 1). The model was adapted by updating the mortality estimates, epidemiology of AF, screening efficacy, and treatment patterns, along with health resource utilization and cost inputs expressed in Canadian currency. Briefly, 2 identical cohorts of patients 65 years and older with no known AF were simulated over their lifetime. At the beginning of the model, one cohort underwent single time point screening with a single-lead ECG device (screening cohort) while the second cohort did not undergo such screening (usual care cohort). Treatment with oral anticoagulants (apixaban, dabigatran, rivaroxaban, and warfarin) was assigned to a proportion of patients with a true-positive AF diagnosis (screening cohort) and a proportion of patients diagnosed with AF via usual care on the basis of the risk of AF development and the likelihood of its detection via routine evaluation. The model compared the screening and usual care cohorts for lifetime incidence of AF, incidence of thromboembolic and bleeding events (ischemic stroke, myocardial infarction, systemic embolism, hemorrhagic stroke, other intracranial hemorrhage, other major bleeds, and clinically relevant nonmajor bleeds), cardiovascular hospitalization, mortality/life years, quality-adjusted life-years (QALYs), and cost (associated with screening, OAC treatment and routine care, and clinical events).

Model inputs

Epidemiology inputs and screening efficacy

Epidemiology inputs were derived from contemporary large pragmatic AF screening studies (Screening for Atrial Fibrillation Via mobile ECG [SAVE]) that had been performed in the Canadian community primary care practice. The methodology and results of the SAVE studies have been previously published.[7,9] Briefly, the SAVE study engaged 133 Canadian primary care physicians who screened a total of 7585 patients 65 years and older for AF with single-lead ECG during routine medical encounters (opportunistic screening). The device detected AF in 270 patients (6.2% of patients screened). The SAVE-2 study expanded on these results by engaging 334 Canadian primary care physicians, who screened a total of 16,817 patients, of whom 1171 patients were diagnosed with AF (7.0%).[9] Institutional review board approval for the present analysis was waived because of the use of retrospective and de-identified data.

Estimation of the impact of a national screening program was ascertained by determining the cohort size under each of the screening and no screening arm on the basis of the total number of general physicians in Canada (89,911),[12] physician participation in the screening rate as indicated in the SAVE study (54.3%),[9] and the number of patients (age $\geq$65 years) screened by each participating physician in a year (60).[9] The resulting collective cohort size was 2,929,301 (89,911*54.3%*60) inclusive of screening and usual care. Age and sex distribution of the cohort were established on the basis of Canadian national statistics for population 65 years and older.[13] Upon AF diagnosis, 82.7% of patients were assumed to receive OAC treatment, consistent with the observations of the SAVE study.[9] Patient distribution for those subjected to OAC treatments was determined by 2017 Canadian market share data (apixaban 51.2%, rivaroxaban 31.6%, dabigatran 7.0%, and warfarin 10.2%).[14]

Risk of clinical events

The Anticoagulants for Reduction In STroke: Observational Pooled analysis on Health outcomes ANd Experience of patientS (ARISTOPHANES) study was used to estimate the clinical event rates (stroke/systemic embolism and bleeding) with apixaban and the comparative efficacy of dabigatran, rivaroxaban, and warfarin.[15] As the ARISTOPHANES study did not provide data on the rates of treatment discontinuation, myocardial infarction, clinically relevant nonmajor, or cardiovascular hospitalization, these data were derived from the Apixaban for Reduction In STroke and Other ThromboemboLic Events in Atrial Fibrillation trial.[16,17] Clinical event rates for patients not receiving OAC treatment were derived from a meta-analysis.[18] Mortality was based on the 2017 Canadian life tables[19] and was adjusted for age and sex.

Model inputs are presented in Online Supplemental Tables 1 and 2.

Costs and utilities

All costs are expressed in 2019 Canadian dollars. A 1-time cost of Can$125 was used as the purchase cost of a smartphone-enabled single-lead ECG device (KardiaMobile, AliveCor, Mountain View, CA), with an additional cost of Can$11.05 assigned to each screening event to account for technical and physician fees.[20] Expenses associated with confirmatory diagnostic testing included cost of a 12-lead ECG (Can$11.05 with interpretation, per screening event) and the additional cost incurred for a general physician office visit (Can$77.20 per screening event), as a conservative assumption.[20] Acquisition costs of OAC treatments were obtained from a provincial drug benefit formulary.[21] A previously published economic evaluation was used to derive the cost of clinical events from a Canadian payer perspective[22–25] and was inflated to 2019 Canadian dollars by using the consumer price index.[26]

For each model health state, life-years are calculated as a sum product of health state membership in each cycle and number of model years, discounted annually using the health outcome discount rate. Total life-years gained by the cohort over the model time horizon was divided by the cohort size to derive the life-years per patient year. QALYs for each model heath state was derived as the sum product of health state membership in each cycle and health state–specific utility value, discounted annually using the health outcome discount rate. The health state utility values were adjusted for relevant utility decrements because of clinical events and treatments patients were receiving, with utility decrements being applied only for the duration affected by the event (eg, stroke having a permanent impact on the health-related quality of life vs bleeding events that only have a temporary impact on the health-related quality of life). Total QALYs gained by the cohort was divided by the cohort size to derive the QALYs per patient year. Because of the lack of Canada-specific utility data, the present analysis uses the utility values obtained from EuroQol 5-dimension catalogue scores by using the Medical Expenditure Panel Survey in the United States.[11]

Detailed inputs of cost and utilities are provided in Online Supplemental Tables 3 and 4 respectively.

Analyses

A deterministic base-case analysis was performed for a cohort of 2,929,301 patients over a lifetime horizon from a Canadian payer perspective, with costs and health outcomes discounted at an annual rate of 1.5% as per the Canadian Agency for Drugs and Technologies in Health economic evaluation guidelines.[27] Indirect costs (eg, productivity loss) were not considered, given the analysis was structured from the payer perspective. Because of the lack of reimbursement for single-lead ECG screening, the cost of the screening program was varied between Can$0.00 and Can$77.20 in scenario analyses. Additional scenario analyses were performed using variations in the base-case cohort size (±25%), single OAC treatment upon diagnosis (apixaban, dabigatran 150 mg twice daily, rivaroxaban, or warfarin), variable prevalence of undiagnosed AF (5.24% vs 6.96%), and variable background detection rates (0%–10%).

Identification of model drivers was achieved using a 1-way sensitivity analysis for key model parameters by varying 1 parameter at a time to its lower or upper bound value around the point estimates used in the base case. A ±25% variation in the base-case values was used to counter the unavailability of 95% confidence interval or standard error. *Incremental net benefit*, defined as the difference between the incremental QALY multiplied by a willingness-to-pay threshold, and incremental costs were calculated on the basis of a threshold of Can$50,000 per QALY. A positive value of incremental net benefit indicates that the intervention (ie, screening) is cost-effective. Probabilistic sensitivity analysis was performed to assess the impact of uncertainty around the model inputs used in the base case. This was carried out by sampling values from the distribution assigned to the key model inputs (eg, gamma for cost inputs and log-normal for hazard ratios), and 1000 model simulations were performed.

Results

Deterministic results

Single time point opportunistic single-lead ECG screening identified an additional 127,670 AF cases when compared with usual care (Table 1). Over a lifetime, the screening cohort experienced fewer cases of ischemic stroke and myocardial infarction (avoidance of 12,326 ischemic stroke cases and 2363 myocardial infarction cases) but a higher number of major bleeding events (additional 30,759 events) when compared with the usual care cohort. The incremental gain of QALYs was 59,577 years in the screening cohort when compared with the usual care cohort.

The screening cohort incurred higher costs associated with screening and OAC therapy than did the usual care cohort (incremental cost of Can$50 million [Can$18 per patient] and Can$1440 million [Can$492 per patient], respectively, over the lifetime). However, the cost of medical events was lower in the screening cohort than in the usual care cohort, which led to a saving of Can$1560 million over lifetime (Table 2).

When considering the total costs of care, the screening strategy resulted in a saving of Can$70 million (Can$22 per patient) over lifetime. Single time point opportunistic single-lead ECG screening was a dominant strategy as compared with no screening because of improved health outcomes at a lower total cost.

Sensitivity and scenario analyses

One-way sensitivity analysis

One-way sensitivity analysis highlighted that the incremental net benefit associated with screening was most sensitive to the uncertainty around the hazard ratio of stroke for patients not receiving any treatment, routine care cost, and hazard

Table 1 Base-case results—clinical outcomes (N = 2,929,301)

Clinical outcomes	Usual care	Opportunistic screening	Incremental (vs usual care)
Screening-related outcomes			
Number of AF detections	345,937	473,607	127,670
Number of screenings	0	2,929,301	2,929,301
Clinical events			
Ischemic stroke*	544,227	527,995	−12,326
Myocardial infarction	128,653	126,291	−2,363
Systemic embolism	27,116	26,291	−825
Hemorrhagic stroke*	14,229	18,208	3,472
Other intracranial hemorrhage	13,075	16,570	3,495
Other major bleeds	580,336	603,630	23,293
CRNM bleeds	122,816	158,044	35,228
Total life-years (per patient)	34,702,736 (11.84)	34,773,489 (11.87)	70,753 (0.02)
Total QALY (per patient)	26,624,75857 (9.08)	26,684,33573 (9.10)	59,577 (0.02)

AF = atrial fibrillation; CRNM = clinically relevant nonmajor; QALY = quality-adjusted life-year.
*Includes recurrent events.

ratio of fatal stroke (Figure 1). Incremental net benefits were positive in all analyses that were performed (range Can$405–Can$1836 per patient), indicating that screening was a cost-effective strategy when compared with no screening in all ranges of parameters at the established willingness-to-pay threshold of Can$50,000 per QALY.

Probabilistic sensitivity analysis

The incremental costs and QALYs calculated for each of the 1000 probabilistic sensitivity analysis simulations for both screening and no screening were plotted on a cost-effectiveness plane (Online Supplemental Figure 2). The outcome of the probabilistic sensitivity analysis suggests that screening was cost-effective (incremental cost-effectiveness ratio vs no screening <Can$50,000 per QALY) in 99.7% of model simulations and was the dominant strategy (eg, less expensive and more effective) in 52.3% of model simulations.

The cost-effectiveness acceptability curve (Online Supplemental Figure 3) demonstrated that screening was an optimal choice for all willingness-to-pay thresholds to achieve maximum net benefit when compared with no screening.

Scenario analysis

The relationship between single-lead ECG screening reimbursement and cost-effectiveness is shown in Figure 2. Overall, a linear relationship was observed between the reimbursement and the incremental cost-effectiveness ratio. The incremental cost-effectiveness ratio remained below the willingness-to-pay threshold of Can$50,000 per QALY for all reimbursements up to Can$1060 per screening event.

Screening was a dominant strategy when reimbursement was ≤Can$30 per screening event, and it remained the dominant strategy except in 2 scenarios: (1) when rivaroxaban was the only treatment option and (2) when AF detection rate in

Table 2 Base-case results—cost outcomes (N = 2,929,301)

Cost outcomes	Usual care	Opportunistic screening	Incremental (vs usual care)
Screening-related	Can$0	Can$0.05 billion	Can$0.05 billion
OAC therapy and routine care	Can$5.62 billion	Can$7.07 billion	Can$1.44 billion
Medical events	Can$49.66 billion	Can$48.10 billion	−Can$1.56 billion*
Total costs	Can$55.28 billion	Can$55.22 billion	−Can$0.07 billion*
Cost outcomes (per patient)			
Screening-related	Can$0.00	Can$17.85	Can$17.85
OAC therapy and routine care	Can$1,919.80	Can$2,412.02	Can$492.23
Medical events	Can$16,952.68	Can$16,420.33	−Can$532.35*
Total costs	Can$18,872	Can$18,850.20	−Can$22.28*
Incremental outcomes vs no screening			
Incremental cost per detected AF		Dominant†	
Incremental cost per stroke avoided		Dominant†	
Incremental cost per LY gained		Dominant†	
Incremental cost per QALY gained		Dominant†	
Incremental net monetary benefit		Can$3.04 billion‡	

AF = atrial fibrillation; LY = life-year; OAC = oral anticoagulant; QALY = quality-adjusted life-year.
*Negative value indicates cost savings with screening.
†Screening is less expensive and more effective.
‡Positive value indicates screening is a cost-effective strategy.

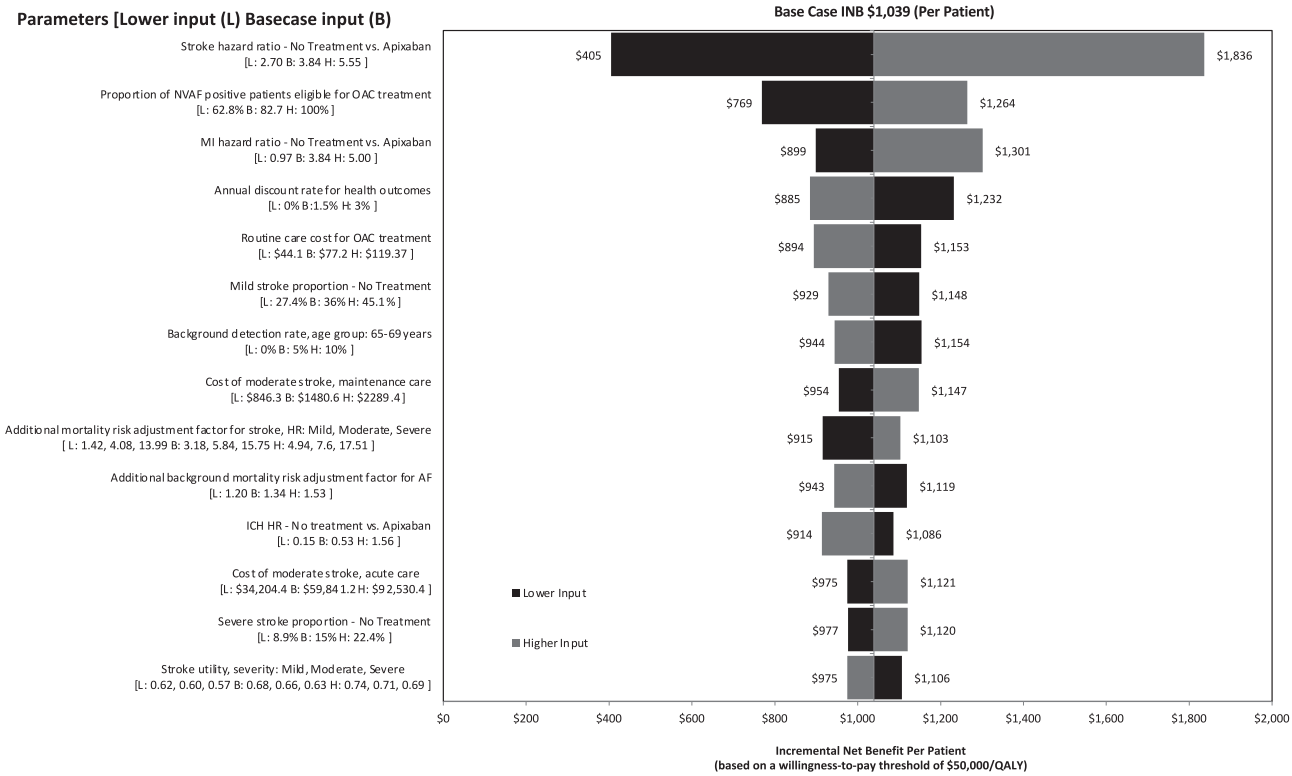

Figure 1 Deterministic sensitivity results—incremental net benefit per patient (screening vs no screening). The *vertical line* intersecting the incremental net benefit (INB) per patient at Can$1039 dollars (based on a willingness-to-pay threshold of Can$50,000 per quality-adjusted life-year) with all parameters set to base-case assumptions. As each parameter is varied across the range provided in parentheses in the left-hand column, *bars* represent the range of incremental cost-effectiveness ratio values obtained. *Black bars* represent the effect of decreasing the parameter relative to its base-case value. *Gray bars* represent the effect of increasing the parameter relative to its base-case value. For example, the INB decreased to Can$769 when the proportion of patients with nonvalvular atrial fibrillation (NVAF) eligible for oral anticoagulation (OAC) therapy was decreased to 62.8% from the base case of 82.7%, and increased to Can$1264 when the proportion of OAC eligible patients was increased to 100%. *Larger bars* suggest that INB is more sensitive to the specific parameter, and *smaller bars* suggest that INB is less sensitive to the parameter. The most influential parameters are found at the top of the graph. AF = atrial fibrillation; HR = hazard ratio; ICH = intracranial hemorrhage; MI = myocardial infarction.

the usual care cohort was 10%. However, even then the incremental cost-effectiveness for these 2 scenarios remained significantly below the willingness-to-pay threshold of Can$50,000 per QALY (ie, Can$60 and Can$310 per QALY for scenarios 1 and 2, respectively).

Discussion

Our model demonstrates that single time point opportunistic screening for AF with a single-lead ECG is a dominant strategy. Specifically, single time point opportunistic screening provided better health outcomes at lower costs in Canadian primary care patients 65 years and older than did usual care. Although associated with increased costs over the patient's lifetime, opportunistic screening led to fewer thromboembolic events (ischemic stroke, systemic embolism, and myocardial infarction) and consequently increased life expectancy and QALYs. Moreover, the increased costs associated with screening (eg, costs associated with screening itself plus the costs associated with OAC treatment of newly detected AF cases and costs associated with bleeding events resulting from an increased number of patients on OACs) were offset by cost savings from the reduced incidence of ischemic stroke, systemic embolism, and myocardial infarction in the screening cohort. To our knowledge, this study is the first of its kind to examine the cost-effectiveness of single-lead ECG screening in Canada using clinical event rates and screening efficacy derived from a large-scale pragmatic screening program conducted in Canadian community practice.[7,9]

Although differences in model structure between studies precludes a direct comparison, these results are consistent with previous analyses performed in several disparate health care jurisdictions.[11,28–32] The Program for the Identification of "Actionable" Atrial Fibrillation demonstrated that screening for AF in a primary care[29] and a pharmacy setting[32] was a cost-effective strategy, with an incremental cost per QALY gained of Can$4788 and Can$7480, respectively, compared with no screening. Similarly, opportunistic AF screening among patients 65 years and older in rural Australia was estimated to be equivalent to AU$16,578 per QALY gained.[28] Likewise, Jacobs et al[31] demonstrated that single-lead ECG screening for AF in patients 65 years and older during seasonal influenza vaccination had a high probability of cost-effectiveness (99.8%) at a €20,000 per QALY willingness-to-pay threshold.

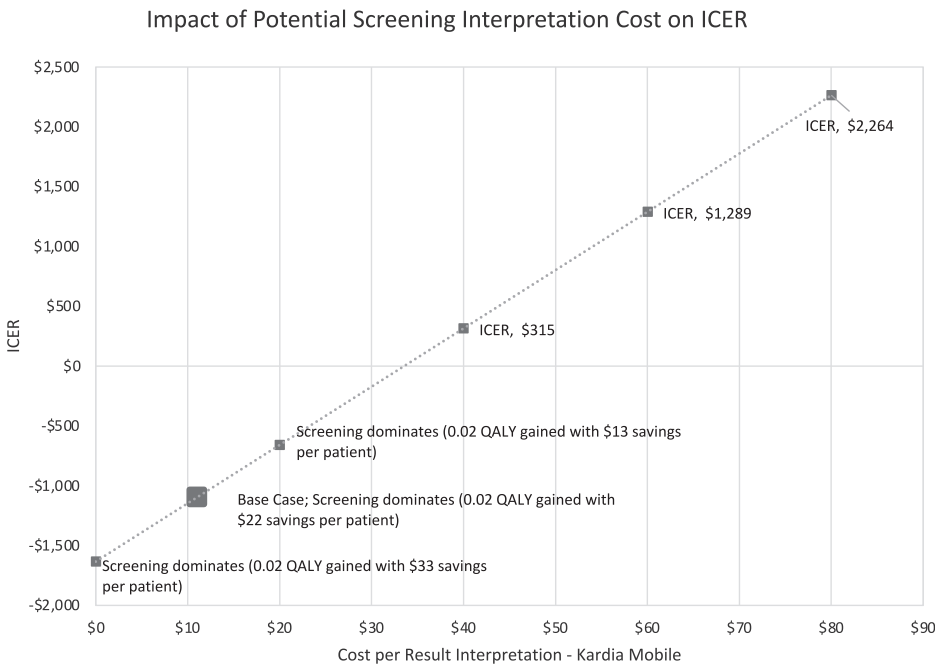

Figure 2 Impact of reimbursement for screening on the incremental cost-effectiveness ratio (ICER) vs no screening. QALY = quality-adjusted life-year.

Areas of remaining uncertainty related to the operationalization of AF screening. In particular, whether AF screening should occur systematically or as opportunistic case finding, the latter being the approach used in the present study. This was addressed in 2 randomized trials performed in a UK primary care setting[33,34]: The first trial randomized 3001 patients older than 65 years to nurse-led single time point systematic screening vs prompted opportunistic case finding.[33] Despite substantially more patients being screened in the systematic arm (73% vs 29%), there was no significant difference in the identification of new AF cases. The Screening for AF in the Elderly study compared 2 interventional groups (single time point systematic screening and opportunistic case finding) to usual care in 50 primary care practices (14,802 patients).[34] Both interventional groups identified significantly more new AF cases compared to usual care; however, only opportunistic case finding was found to be cost-effective.[34]

Limitations

As with any simulation study, the findings should be evaluated in the context of assumptions and limitations. Our study observed a better outcome with screening predominantly because of the high rate of undiagnosed AF. While the true prevalence of undiagnosed AF is unknown, we used the rates observed in a contemporary pragmatic AF screening studies performed in Canadian community primary care.[9] It is likely that the cost-effectiveness of screening would be limited by a lower prevalence of undiagnosed AF detected by screening or a higher prevalence of AF detected by conventional means; however, our sensitivity analyses suggested that screening remained cost-effective across variable prevalences. Moreover, as the present study employed inputs based on single time point screening, it is possible that it employed an underestimate of the true background prevalence. Specifically, the STROKESTOP study demonstrated that repeated rhythm assessments conferred a 4-fold increase in AF detection over single time point screening.[35] Because of the lack of reimbursement code for single-lead ECG interpretation, we used the cost associated with the interpretation of a 12-lead ECG in the primary analysis; however, our scenario analyses suggest screening to be a cost-effective strategy over a reimbursement range of Can$11.20–Can$77.20 per screening event. Baseline patient characteristics such as comorbidities, risk factors, and $CHADS_2$ score distribution were derived from a multinational clinical trial (Apixaban for Reduction In STroke and Other ThromboembolLic Events in Atrial Fibrillation) and a prospective observational study (ARISTOPHANES). Likewise, the rates of stroke, systemic embolism, and intracranial hemorrhage were derived from the observational ARISTOPHANES study,[15] which was based on US claims databases. Thus, the analyses presented in this study assumed that these patient characteristics and clinical outcomes were applicable to the Canadian population. Moreover, while OAC adherence was not directly considered within the model, we assumed that adherence would be consistent with the US claims data used to inform the event rates employed as model inputs. While nonadherence would be expected to limit the absolute benefit of OAC therapy, as the impact of nonadherence would be observed in both groups it is unlikely to substantially alter the conclusions of the study. Finally, there is a lack of randomized clinical trials establishing a causal

relationship between AF screening and prevention/reduction of stroke and other clinical events. This is a common limitation for all cost-effectiveness simulations, and thus the results from such studies should be considered hypothesis-generating until prospective empirical evidence is available.

Conclusion

Our study demonstrates that single time point opportunistic screening of AF using single-lead ECG is cost-effective in Canadian patients 65 years and older. Compared with usual care, opportunistic screening was a dominant strategy because of the ability to diminish future health expenditures, a finding that is relevant to single-payer health systems. These results were consistent over a wide range of potential reimbursement, although affected by AF detection rates.

Acknowledgments

Editorial support was provided by Lauren Randall MS, of Evidera, supported by Bristol Myers Squibb.

Funding Sources: Funding for this study was provided by Bristol Myers Squibb, Princeton, NJ.

Disclosures: Dr Andrade reports grants and personal fees from Medtronic, Bristol Myers Squibb (BMS), Pfizer, Bayer, and Servier. Mr Shah, Dr Kongnakorn, and Ms Brown are employees of Evidera, who were paid consultants to BMS in relation to this study. At the time of study, Ms Lanitis was an employee of Evidera. Drs Godin and Dhanda are employees of BMS. Dr Nault reports speakers and consultant honoraria from BMS-Pfizer, Bayer, Servier, Biosense Webster, and Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Because of the use of retrospective and de-identified data in this study, patient consent was not required.

Ethics Statement: Institutional Review Board approval for the present analysis was waived because of the use of retrospective and de-identified data.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2022.11.003.

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