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Economic evaluation of extended electrocardiogram monitoring for atrial fibrillation in patients with cryptogenic stroke

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Abstract

Background: Timely identification of occult atrial fibrillation following cryptogenic stroke facilitates consideration of oral anticoagulation therapy. Extended electrocardiography monitoring beyond 24 to 48 h Holter monitoring improves atrial fibrillation detection rates, yet uncertainty remains due to upfront costs and the projected long-term benefit. We sought to determine the cost-effectiveness of three electrocardiography monitoring strategies in detecting atrial fibrillation after cryptogenic stroke.

Methods: A decision-analytic Markov model was used to project the costs and outcomes of three different electrocardiography monitoring strategies (i.e. 30-day electrocardiography monitoring, three-year implantable loop recorder monitoring, and conventional Holter monitoring) in acute stroke survivors without previously documented atrial fibrillation.

Results: The lifetime discounted costs and quality-adjusted life years were $206,385 and 7.77 quality-adjusted life years for conventional monitoring, $207,080 and 7.79 quality-adjusted life years for 30-day extended electrocardiography monitoring, and $210,728 and 7.88 quality-adjusted life years for the implantable loop recorder strategy. Additional quality-adjusted life years could be attained at a more favorable incremental cost per quality-adjusted life year with the implantable loop recorder strategy, compared with the 30-day electrocardiography monitoring strategy, thereby eliminating the 30-day strategy by extended dominance. The implantable loop recorder strategy was associated with an incremental cost per quality-adjusted life year gained of $40,796 compared with conventional monitoring. One-way sensitivity analyses indicated that the model was most sensitive to the rate of recurrent ischemic stroke.

Conclusions: An implantable loop recorder strategy for detection of occult atrial fibrillation in patients with cryptogenic stroke is more economically attractive than 30-day electrocardiography monitoring compared to conventional monitoring and is associated with a cost per quality-adjusted life year gained in the range of other publicly funded therapies. The value proposition is improved when considering patients at the highest risk of recurrent ischemic stroke. However, the implantable loop recorder strategy is associated with increased health care costs, and the opportunity cost of wide scale implementation must be considered.

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Introduction

Atrial fibrillation (AF) is an important risk factor for ischemic stroke, and up to a third of cryptogenic stroke is associated with occult paroxysmal AF.[1,2] Although the temporal correlation between stroke and AF is unclear,[3] identifying the subset of cryptogenic stroke survivors with occult AF is immediately relevant because treatment with oral anticoagulation (OAC) will reduce the risk of recurrent stroke and death in the either primary or secondary prevention setting.[4] Importantly, OAC does not confer the same benefit in stroke survivors without AF or other sources of cardiac embolism and is associated with harm and an increased risk of major bleeds.[5]

Episodic or paroxysmal AF detection depends directly on the duration of monitoring. Use of serial ECG or 24-h and 48-h Holter monitoring provides suboptimal detection of AF with diagnostic rates of less than 5%. Improved AF detection (>20% of AF episodes) is possible with 30-day ECG monitoring or prolonged monitoring (≥two years) with implantable loop recorders (ILR).[2,6]

Uncertainty remains with regard to wide scale adoption of these technologies because longer term monitoring is expensive. Prior economic evaluations have shown that prolonged ECG monitoring (i.e. 30-day monitoring or ILR) may be cost-effective versus 24 to 48 h of ambulatory ECG (Holter) monitoring, the current standard of care for AF detection.[7,8] However, limited data exist to suggest an optimal extended monitoring strategy, as prior economic evaluations have not directly compared 30-day monitoring to an ILR-monitoring strategy.[9] Comparisons between different ECG monitoring technologies are limited due to the heterogeneity in the design and assumptions in these prior economic models.

We conducted a cost–utility analysis directly comparing three ECG monitoring strategies, (a) ILR, (b) 30-day extended electrocardiogram (ECG) monitoring, and (c) conventional monitoring (24- to 48-h Holter), in detecting occult paroxysmal AF in patients surviving a transient ischemic attack (TIA) or ischemic stroke of unknown etiology.

Methods

The study protocol and report were prepared in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement.[10] Formal ethical review was not required by Conjoint Health Research Ethics Board at the University of Calgary for model-based studies using secondary data from the published literature.

Model design and structure

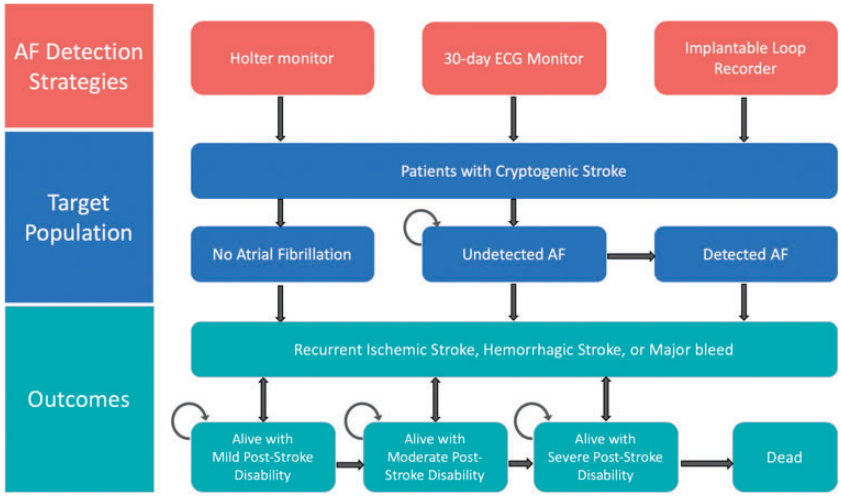
We performed a cost–utility analysis to project the outcomes and costs of three ECG monitoring strategies: (a) 30-day extended ECG monitoring, (b) ILR with up to three years of continuous ECG monitoring, and (c) conventional monitoring (24 to 48-h Holter). The study population included a simulated cohort of 62-year-old Canadian women and men presenting to a hospital with acute stroke or TIA, without previously documented AF at time of index presentation or following in-hospital Holter monitoring, and in whom additional cardiac monitoring would be desired to screen further for the possibility of paroxysmal AF.

A state-transition Markov model was developed in consultation with clinical experts in TreeAge Pro 2020 (Williamstown, MA). A lifetime horizon was adopted to ensure that all relevant costs, life years (LYs), and quality-adjusted life years (QALYs) were obtained over three-month cycles. To account for differences in recurrent stroke risk, the Markov model included four categories of health states that considered the various combinations of disease: (a) AF detected and treated with anticoagulation, (b) AF detected and treated with aspirin, (c) occult AF not detected and treated with aspirin, and (d) no underlying AF present. The risks of recurrent ischemic stroke, hemorrhagic stroke, or major extracranial hemorrhage were adjusted on the safety and efficacy of treatment received (i.e. aspirin, warfarin, or direct oral anticoagulant (DOAC)), and the cohort's risk of subsequent stroke, which varied depending on the presence of underlying AF.

All patients entered the model with ''no underlying AF'' or ''occult AF not detected.'' Depending on the diagnostic performance of the allocated ECG monitoring strategy, AF could be subsequently detected, and patients could be initiated on appropriate therapy (i.e. anticoagulation with warfarin or DOACs). If subsequent testing for AF was non-diagnostic, patients received aspirin alone (Figure 1).

To account for differences in costs, quality of life, and post-stroke mortality, we further stratified the disease-treatment health states based on mild, moderate,

Figure 1. Structure of Markov model, showing atrial fibrillation (AF) detection strategies and outcomes that were considered in this cost–utility analysis.



or severe post-stroke disability as classified by the Modified Rankin Scale (mRS). The mild, moderate, and severe disabilities were defined as a mRS score of 0–2, 3–4, and 5, respectively. Thus, a total of 13 health states (including mRS 6 or death) were included in the model.

Model assumptions

Consistent with prior cost-effectiveness analyses of anticoagulants for stroke prevention in AF, we made several model assumptions.[11] First, after an intracranial hemorrhage, all patients on anticoagulation would switch to aspirin. After a major bleed, a quarter of patients would discontinue anticoagulation permanently. Second, patients who experience a recurrent ischemic or hemorrhagic stroke could only transition to a health state with similar or greater disability; for example, stroke survivors with moderate disability (mRS 3–4) could develop severe disability with recurrent stroke (mRS 5), but they could not move into a health state with mild disability (mRS 0–2) in subsequent cycles. Based on national trends in the prescribing anticoagulants for AF,[12] we assumed that 60% of patients on anticoagulation received a DOAC and 40% received warfarin.

Model inputs

The clinical effectiveness and diagnostic performance of ILRs and 30-day ECG monitors were obtained from two randomized clinical trials: CRYSTAL AF (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke), which compared AF detection rates between ILRs and conventional Holter monitoring[2]; and EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event Study), which compared 30-day extended ECG monitors to conventional monitoring.[6]

AF detection with conventional monitoring was derived from the Kaplan–Meier curves in the CRYSTAL AF trial, in which AF detection at three years was 3.0%. Since, ongoing trials comparing ILRs to 30-day ECG monitoring in patients with cryptogenic stroke have yet to be published, an indirect comparison was made. The relative risk from the EMBRACE trial was applied to the three-month cycle AF detection rate of patients receiving the Holter monitoring strategy to estimate AF detection for patients with the 30-day ECG monitoring strategy. That is, the proportion with detected AF at three months was 1.0% with the Holter monitor strategy. We then applied the relative risk of 4.9 (for 30-day monitor vs Holter) reported in the EMBRACE trial to derive the three-month AF detection rate with 30-day monitoring. After converting the three-month rate back to a proportion, AF detection at three months was 4.8% among patients receiving the 30-day monitor. For subsequent cycles, we assumed that additional AF detection occurred at the same rate as the conventional follow-up arm of the CRYSTAL AF trial. The CRYSTAL AF hazard ratio for additional AF detection with ILRs compared to convention monitoring was applied to the cycle-specific conventional monitoring rates to estimate AF detection in patients receiving an ILR.

The CRYSTAL AF and EMBRACE trials detected subclinical (or short-lasting, asymptomatic) paroxysmal AF in patients with cryptogenic stroke. The risk of recurrent ischemic stroke in patients with subclinical AF is unclear. In patients with non-anticoagulated

cryptogenic stroke, the annual recurrent ischemic stroke risk is approximately 9% to 10% in the age group under consideration.[13] Assuming that patients with subclinical AF have approximately half the risk of ischemic stroke compared to patients with clinical AF, we used a more conservative annual stroke rate of 5% for our base case and varied this rate with a large range (2 to 10%) in our sensitivity analyses to explore the uncertainty in this estimate.[14]

Costs were assessed from the perspective of the Canadian public healthcare payer. Three main categories of costs were included: ECG monitoring device costs, outpatient costs of managing stroke survivors (including costs of medication, home care services, long-term care, emergency department visits, and rehospitalization for non-stroke related events), and costs associated with acute adverse health events (including hospitalization costs, rehabilitation, and the costs of outpatient care within the first year (Supplemental Table S1). All costs were valued in 2018 Canadian dollars and adjusted using the general Consumer Price Index for goods and services (if required).[15]

Utility measurements (i.e. overall measures of quality of life) were obtained from a United Kingdom population-based study of stroke survivors, the Oxford Vascular (OXVASC) Study, and previously published models on anticoagulation in AF.[16,17] A decrement was applied for major bleeding events, which was transiently applied only during the cycle when it occurred.[8]

Variability and uncertainty

One-way sensitivity analyses varied a single input parameter at a time and recorded the change in incremental cost per QALY. A probabilistic sensitivity analysis was also performed, where a Monte Carlo simulation of 10,000 iterations was used to propagate the uncertainty in individual model parameters to generate a distribution of expected costs and QALYs. Several additional analyses were prespecified including a scenario analysis considering the use of only DOACs for anticoagulation, scenario analyses that varied the duration of ILR monitoring, and a two-way sensitivity analyses exploring the clinical uncertainty in recurrent ischemic stroke risk in the AF detected and anticipated clinical effect of anticoagulation. Costs and health outcomes were accrued through a lifetime horizon at a discount rate of 1.5% as per contemporary Canadian guidelines for economic evaluation.[18]

Results

Model validation

The survival probabilities were estimated for the ECG detection strategy representing the current standard of care (i.e. 24- to 48-h Holter monitoring strategy). The one-, three-, and five-year modeled survival probabilities were 94%, 82%, and 72%, respectively, and were similar to those reported in a longitudinal cohort of stroke survivors from Ontario with reported survival of 95% at one year, 84% at three years, and 74% at five years.[19] Additionally, the modeled survival probabilities were comparable to those reported in cryptogenic stroke survivors from the Oxfordshire cohort: 94% at one year and 75% at five years.[13] The modeled AF detection rates for the ILR and conventional Holter monitoring strategies were comparable to the detection rates reported in CRYSTAL AF (Figure 2).[2]

Base case results

Patients with cryptogenic stroke who underwent a strategy of conventional monitoring gained an average of 7.77 QALYs or 11.00 LYs at a total cost of $206,385. Both extended ECG monitoring strategies were associated with additional QALYs at increased costs; the lifetime discounted costs and QALYs were $207,080 and 7.79 QALYs for the 30-day extended ECG monitor, and $210,728 and 7.88 QALYs for the ILR strategy (Table 1).

Both 30-day and ILR monitoring strategies were associated with higher costs, due to initial upfront device costs and the costs due to increased bleeding events associated with higher rates of anticoagulation initiation. These costs were offset by the cost-savings from prevented recurrent ischemic strokes. Compared to conventional Holter monitoring, our model predicted that 70 ischemic strokes would be prevented at the expense of 8 hemorrhagic strokes and 10 major gastrointestinal (GI) bleeds for every 1000 patients screened with an ILR. The 30-day ECG monitoring strategy would prevent 10 ischemic strokes at the expense of one hemorrhagic stroke and one major GI bleed for every 1000 screened patients compared to conventional monitoring.

The ILR strategy was associated with the more favorable incremental cost-effectiveness ratio (ICER) of $40,796 per QALY gained, compared with conventional monitoring, whereas 30-day monitoring estimated an ICER of $42,707 per QALY gained. Additional QALYs could be attained at a more favorable incremental cost per QALY with the ILR strategy, thereby eliminating the 30-day strategy by extended dominance.

Model uncertainty

The one-way sensitivity analyses demonstrated that the uncertainty in several variables may affect the value proposition of the ILR strategy compared to conventional monitoring (Figure 3).

Figure 2. Simulated atrial fibrillation detection rates from model compared with reported detection rates from CRYSTAL-AF study.
Solid lines: simulated AF detect rates from Markov model; orange dots: AF detection rates with Holter monitoring strategy from CRYSTAL AF trial; blue triangles: AF detection rates with ILR from CRYSTAL AF Trial. EMBRACE did not report AF detect rates beyond one year (after the initial increased AF detection at three months, we assumed a similar rate of incremental detection as the Holter monitoring strategy beyond three months to three years).

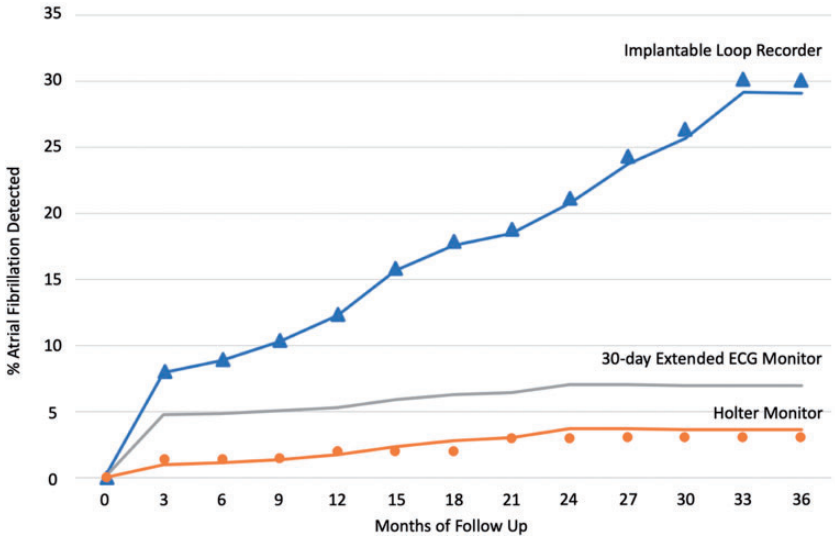


Table 1. The incremental cost per life year and cost per QALY when comparing three strategies of extended ECG monitoring (referencing conventional monitoring as the baseline comparator)

	Total costs ($)	Total life years	Total QALYs	ICER ($ per QALY gained)
Conventional monitoring	206,385	11.00	7.77	–
30-day extended ECG monitor	207,080	11.02	7.79	42,707
Implantable loop recorder	210,728	11.12	7.88	40,796

QALY: quality-adjusted life year; ICER: incremental cost effectiveness ratio; ECG: electrocardiogram.

The model inputs with the greatest variation effect on the estimated ICERs included the clinical effectiveness and safety of anticoagulation, discounting rate, and the annual rate of recurrent ischemic stroke. For example, at a low recurrent ischemic stroke risk of 4% per year, an ILR-monitoring strategy yielded a cost per QALY gained of $52,514. Conversely, at higher ischemic stroke rates (i.e. 10% per year), the cost per QALY gained for the ILR-monitoring strategy was $25,261. Despite this variation in cost per QALY gained, ILR-monitoring remained the cost-effective strategy compared to both 30-day extended ECG monitoring or conventional Holter monitoring, at a willingness-to-pay threshold of $50,000 per QALY. The model was also sensitive to the discounting rate, which likely was due to the clinical benefits (i.e. recurrent strokes prevented) occurring later in time.

We conducted a two-way sensitivity analysis to further describe how the estimated ICERs varied across a range of assumptions for annual ischemic stroke risk on ASA and effectiveness of anticoagulation in preventing recurrent stroke (Supplemental Figure S1). At a willingness-to-pay threshold of $50,000 per QALY gained, an ILR-monitoring strategy would remain economically favorable as long as the recurrent annual ischemic stroke rate was 3.3% or greater assuming maximal anticoagulation effectiveness. At threshold of $100,000 per QALY gained, ILR-monitoring was the primarily favored strategy regardless of assumptions in ischemic stroke rate or anticoagulation effectiveness.

Figure 3. Tornado diagrams summarizing one-way sensitivity analyses on cost per quality-adjusted life years comparing implantable loop recorder and Holter monitor.

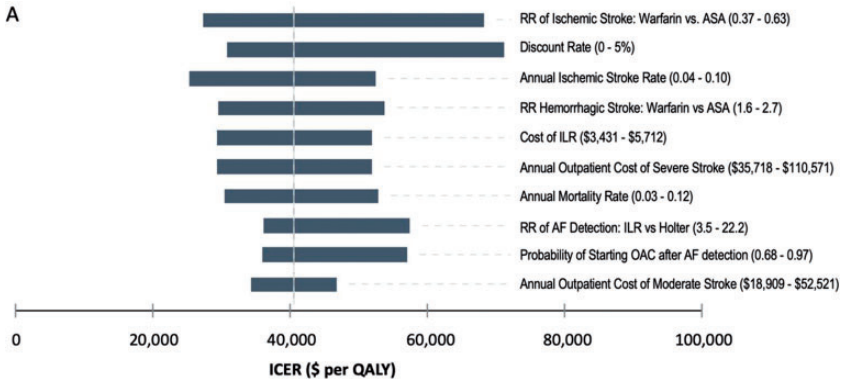
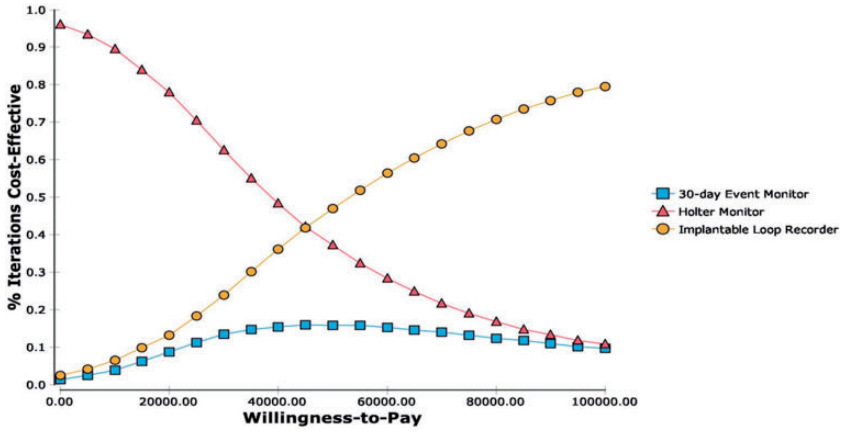


Figure 4. Cost-effectiveness acceptability curves.



The cost-effectiveness acceptability curve depicts the probability of each strategy having the best net health benefit at different willingness-to-pay thresholds (Figure 4). At a threshold of $50,000 per QALY gained, an ILR-monitoring strategy had the best net health benefit in 49% of simulations, whereas the 30-day monitoring strategy had a 17% probability of being cost-effective. At a threshold of $100,000 per QALY gained, the ILR-monitoring strategy was the most cost-effective approach in 83% of simulations.

Scenario analyses

Given trends of increasing utilization of DOACs over warfarin, we modeled an optimistic scenario with DOACs as the anticoagulant of choice due to their improved clinical safety profile and equivalent clinical effectiveness compared to warfarin. This scenario analysis found a similar value proposition for either 30-day extended ECG monitoring or ILR-monitoring strategies at a cost per QALY gained of $35,265 and $36,126, respectively, compared to conventional monitoring (Supplemental Table S2).

Since AF detection rates vary by the duration of ILR monitoring, we sought to better understand the duration of monitoring required for an ILR strategy to be economically attractive. We conducted a scenario analysis to explore the value proposition of 12 months and 24 months of ILR monitoring. While both 12 months and 24 months of ILR monitoring were associated with additional QALYs compared to conventional Holter monitoring, the estimated ICERs were $86,531 per QALY gained and $61,041 per QALY gained, respectively (Supplemental Table S3). That is, a shorter duration of ILR monitoring was associated with an increased ICER due to the smaller incremental

QALY gains relative to the incremental lifetime costs associated with an ILR strategy. Importantly, the 30-day monitoring strategy was no longer dominated and considered more economically attractive at $42,707 per QALY gained.

Discussion

Main findings

Our study found that the incremental cost per QALY was $40,796 for an ILR-monitoring strategy of three years compared to conventional follow up, while the 30-day monitoring strategy was removed by extended dominance, since incremental QALYs could be purchased for less with the ILR strategy. The ILR-monitoring strategy yielded a cost per QALY gained within the range of other publicly funded therapies and previously accepted willingness-to-pay thresholds in Canada (i.e. $50,000 or $100,000 per QALY).[20] Interestingly, the ILR-monitoring strategy was the most economically attractive strategy only when continuous monitoring was obtained over a three-year period. With monitoring durations of less than three years, the 30-day monitoring strategy was no longer extendedly dominated and also considered economically attractive.

Prior economic studies

Several prior economic studies have performed pairwise comparisons of 30-day extended monitoring or ILR-monitoring with conventional monitoring.[7,8,21,22] These studies report a wide variation in the ICER estimates; for example, Yong et al.[8] found that 30-day monitoring was cost-effective with an ICER of $2000 per QALY gained (2014 USD), whereas, a model developed by the Canadian Agency for Drug and Technologies in Health (CADTH) estimated an ICER of $185,613 per QALY gained.[21]

Limitations of these prior studies include the use of Markov model structures that did not include all relevant health events, the underestimation of costs and health resource utilization associated with health events, and inadequate model calibration. For example, CADTH estimated an overall life expectancy of 4.3 to 4.6 years among stroke survivors with underlying AF over the lifetime horizon of their model. However, their model was calibrated to the Oxfordshire study that reported five-year survival rather than overall life expectancies.[16] In our study, a de novo model was extensively validated to both the Oxfordshire cohort and a more contemporary Canadian poststroke cohort.[13,19] Thus, our model projected a more consistent five-year life expectancy of 4.1 years.

Our results are more comparable with the cost-effectiveness analyses reported from other countries that compared a strategy of ILR-monitoring to conventional follow up, yielding incremental cost-effectiveness ratios of £17,175 (2013 British pounds) per QALY gained, and Australia $29,570 (2017 Australian Dollar) per QALY gained, respectively.[7,22]

Uncertainty of recurrent stroke rate

As previously described, our model was sensitive to the rate of recurrent ischemic stroke and presumed efficacy of anticoagulation in the setting of device-detected AF. Higher ischemic stroke rates tended to yield more attractive ICERs since a greater proportion of ischemic stroke and downstream costs are prevented through extended ECG monitoring and AF diagnosis. We assumed a more conservative 5% annual recurrent ischemic stroke rate, compared to historically reported rates of 10% based on the meta-analyses of landmark anticoagulation trials comparing aspirin to warfarin.[4] The patients enrolled in these trials likely had a relatively high AF burden to be detected by sporadic 12-lead ECG monitoring. With the advent of continuous extended monitoring devices, it is unclear the degree of AF burden required to confer a similar stroke risk as AF diagnosed by a single 12-lead ECG. While the ischemic stroke risk is elevated in patients with device-detected AF compared with the general population, prior observation studies have noted lower absolute stroke rates compared to the rates attributed to AF diagnosed by an opportunistic 12-lead ECG.[23] However, these observational studies were limited by concomitant anticoagulation for device-detected AF, and variable inclusion of patients with prior recent stroke or TIA, which may further limit the generalizability of observed stroke risk. Nevertheless, our results relied on the conservatively lower rate of recurrent ischemic stroke in our ICER estimation.

Clinical implications

While the ICER is a summary measure to aid clinicians and decision-makers when comparing across different technologies, these comparisons are limited by variations in the modeling assumptions and methodologic rigor. Our study provides a direct comparison of three ECG monitoring strategies, which may help facilitate health policy decisions regarding the optimal extended ECG monitoring strategy. Importantly, although an ILR-monitoring strategy may be associated with a similar cost per QALY as other publicly funded treatments, ILRs are not cost-saving. That is, an ILR monitoring

strategy is associated with increased healthcare costs, and the opportunity cost of wide scale implementation should be considered.

Limitations

This study has limitations including the lack of clinical effectiveness studies that directly compare the AF detection rates between 30-day extended ECG monitors, ILRs and conventional follow up. Furthermore, our model was based on the clinical effectiveness results of only two moderately sized randomized controlled trials, EMBRACE and CRYSTAL AF. Nevertheless, recent real-world cohort data corroborate the detection rates reported in CRYSTAL AF.[24] Another limitation of the study is that micro-costing data were not available as inputs in our model, and there was uncertainty regarding the estimated long-term follow up costs of annual stroke care. However, these costs did not seem to significantly affect our model estimates in our sensitivity analyses.

Conclusion

The use of ILRs for detection of occult AF in patients with cryptogenic stroke is associated with a cost per QALY gained in the range of other publicly funded therapies. The value proposition is improved when considering patients at the highest risk of recurrent ischemic stroke. Nevertheless, the ILR monitoring strategy is associated with increased healthcare costs, and the opportunity cost of wide scale implementation must be considered.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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