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Potential Cost-Effectiveness of Ambulatory Cardiac Rhythm Monitoring After Cryptogenic Stroke

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Original Contribution

Potential Cost-Effectiveness of Ambulatory Cardiac Rhythm Monitoring After Cryptogenic Stroke

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Background and Purpose—Prolonged ambulatory ECG monitoring after cryptogenic stroke improves detection of covert atrial fibrillation, but its long-term cost-effectiveness is uncertain.

Methods—We estimated the cost-effectiveness of noninvasive ECG monitoring in patients aged ≥55 years after a recent cryptogenic stroke and negative 24-hour ECG. A Markov model used observed rates of atrial fibrillation detection and anticoagulation from a randomized controlled trial (EMBRACE) and the published literature to predict lifetime costs and effectiveness (ischemic strokes, hemorrhages, life-years, and quality-adjusted life-years [QALYs]) for 30-day ECG (primary analysis) and 7-day or 14-day ECG (secondary analysis), when compared with a repeat 24-hour ECG.

Results—Prolonged ECG monitoring (7, 14, or 30 days) was predicted to prevent more ischemic strokes, decrease mortality, and improve QALYs. If anticoagulation reduced stroke risk by 50%, 30-day ECG (at a cost of USD $447) would be highly cost-effective ($2000 per QALY gained) for patients with a 4.5% annual ischemic stroke recurrence risk. Cost-effectiveness was sensitive to stroke recurrence risk and anticoagulant effectiveness, which remain uncertain, especially at higher costs of monitoring. Shorter duration (7 or 14 days) monitoring was cost saving and more effective than an additional 24-hour ECG; its cost-effectiveness was less sensitive to changes in ischemic stroke risk and treatment effect.

Conclusions—After a cryptogenic stroke, 30-day ECG monitoring is likely cost-effective for preventing recurrent strokes; 14-day monitoring is an attractive value alternative, especially for lower risk patients. These results strengthen emerging recommendations for prolonged ECG monitoring in secondary stroke prevention. Cost-effectiveness in practice will depend on careful patient selection. **(*Stroke*. 2016;47:00-00. DOI: 10.1161/STROKEAHA.115.011979.)**

Key Words: anticoagulant ■ atrial fibrillation ■ electrocardiography ■ secondary prevention ■ stroke

Identification and treatment of atrial fibrillation (AF) is a key priority in the secondary stroke prevention management of patients with ischemic stroke or transient ischemic attack (TIA). One in every 4 patients with ischemic stroke has no specific cause evident after standard investigations (cryptogenic), and the usual treatment is antiplatelet therapy.[1] Paroxysmal AF is often suspected in patients with cryptogenic embolic strokes, but it routinely goes underdiagnosed and undertreated in practice because screening methods have typically been limited to short-duration (eg, 24 hours) ECG monitoring post stroke.[2]

Prolonged ambulatory monitoring has become increasingly feasible with recent advances in ECG device technologies, and it has now been shown in randomized trials to significantly improve AF detection and lead to increased anticoagulant treatment rates in patients with stroke or TIA.[2–4] However, its cost-effectiveness is uncertain and likely varies by device, monitoring duration, and patient characteristics.[5–8] Such data are needed to inform clinical practice and health policy decisions about the optimal monitoring strategies for secondary stroke prevention. Decision analytic modeling can provide insights into the comparative long-term clinical and

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cost-effectiveness of prolonged ECG monitoring by combining available evidence.

Our primary objective was to estimate the potential cost-effectiveness of 30-day ECG monitoring (using an external auto-triggered event loop recorder) after a cryptogenic stroke or TIA and an initial negative 24-hour Holter ECG, compared with a repeat 24-hour ECG (Holter). Our secondary objectives were to assess the cost-effectiveness of 7-day and 14-day ECG against a repeat 24-hour ECG. We conducted an economic evaluation using data from the EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) trial of 30-day noninvasive ECG monitoring in this population,[3] combined with data from the published literature.

Methods

We constructed a Markov cohort model to simulate disease progression of patients who experienced a cryptogenic ischemic stroke or TIA within the preceding 6 months (Figure I in the online-only Data Supplement). Patient characteristics were based on the EMBRACE trial cohort (Table 1).[3] In the base case, the analysis adopted a lifetime horizon. Patients entered the Markov model in the no event health state. The monitoring strategy determined the odds of detecting AF; patients' AF and treatment status determined the clinical event rates (ischemic stroke, intracranial hemorrhage, major bleeding, and mortality). Patients' quality of life declined after a clinical event. As patients moved through different health states every year, they accrued direct healthcare costs, life-years, and quality-adjusted life-years (QALYs). The risk of ischemic stroke and intracranial hemorrhage increased with age.[9,10] Stroke severity was classified according to the modified Rankin Scale. We discounted future clinical outcomes and costs at 5% per year.[11]

Assumptions

To simplify the model, we made several assumptions that are consistent with those in previous cost-effectiveness analyses of anticoagulants for stroke prevention in AF[9,12]: (1) the efficacy of treatment remained constant over time unless patients discontinued treatment; (2) after an intracranial hemorrhage or major bleed, patients would switch to aspirin; and (3) patients who had a recurrent stroke or intracranial hemorrhage could only move to a health state with similar or greater disability; for example, patients with a mild stroke could develop a moderate stroke but not vice-versa.

AF Detection and Treatment Rates

Detection rates were based on the observed primary outcome in EMBRACE: episodes of AF ≥30 s detected within 90 days after randomization (Table 1).[3] In the EMBRACE intervention group, half of the AF cases were detected within the first 7 days of monitoring, and three quarters were detected within 14 days of monitoring.[3] In that trial, 89% of patients with AF detected received an oral anticoagulant[3]; in sensitivity analysis, we varied this rate between 50% and 100%. We assumed 25% of anticoagulated patients received warfarin and 75% received a novel oral anticoagulant in the base case and varied novel oral anticoagulant use (25% to 100%) in sensitivity analyses.[13] This assumption was based on recent practice patterns and expert opinion by clinicians to best reflect the current and future use of novel oral anticoagulants versus warfarin for such patients.

Clinical Event Rates

EMBRACE detected mostly subclinical paroxysmal AF in patients with cryptogenic stroke.[3] The annual risk of recurrent ischemic stroke in nonanticoagulated cryptogenic stroke patients is ≈3% to 8%[1,14]; the risk among those with subclinical AF is very likely higher than the average, but the exact rate is uncertain.[15] In patients with previous stroke or TIA and clinical AF (and similar $CHADS_2$ scores as the EMBRACE cohort) receiving aspirin, the estimated annual rate is ≈9%.[3,16–18] We used a lower stroke risk (4.5% per year) for the base case, assuming that patients with subclinical AF have half the risk of ischemic stroke than patients with clinical AF.[19,20] This estimate is also in line with the rate (4.8%) observed in subclinical AF patients with previous stroke or TIA (Jeff Healey, unpublished data, 2014).[20] We varied this rate (2.5%–8.0%) in 1- and 2-way sensitivity analyses. Also, to reflect the uncertainty in this estimate, we assigned a larger confidence interval in probabilistic sensitivity analysis (Table I in the online-only Data Supplement).

For the base case, we estimated that oral anticoagulant therapy would reduce ischemic stroke risk by 50% over aspirin (Methods section in the online-only Data Supplement).[17,21–23] The exact relative risk reduction is uncertain for subclinical AF because most patients with AF in anticoagulant trials had clinical AF; therefore, we varied the relative risk reduction (20%–60%) in sensitivity analyses and assigned a larger confidence interval in probabilistic sensitivity analysis.

Rates of intracranial hemorrhage (1.07% per year) and major bleeding (4.6% per year) for warfarin were estimated from patients with previous stroke or TIA receiving warfarin (Methods section in the online-only Data Supplement).[24–27] Aspirin and novel oral anticoagulants had lower risks of intracranial hemorrhage and major bleeding than warfarin.[17,28,29] Mortality was age and sex specific.[30] The target population had a higher risk of death than the general population (hazard ratio, 2.0); patients who had moderate to severe disability after stroke or intracranial hemorrhage had higher mortality risk than those with minor stroke or intracranial hemorrhage (hazard ratio, 2.0).[31–34]

Costs and Utilities

The analysis was undertaken from the perspective of a public healthcare payer. In addition to AF monitoring costs, health state costs included costs of medication, international normalized ratio monitoring, hospitalizations, physician services, emergency department visits, rehabilitation, home care, and long-term care (Methods section and Table II in the online-only Data Supplement). The first-year costs for ischemic stroke and intracranial hemorrhage came from studies of stroke costs[35,36] and cost-effectiveness of anticoagulants for stroke prevention.[12,33] Subsequent year costs were 60% of the first-year costs, based on long-term costing of stroke.[33,37] The analysis used

Table 1. Model Inputs for the Base Case and Deterministic SA

Variable	Base Case (SA)
Patient characteristics	
Starting age, y	73 (55–80)
Sex (% female)	50%
$CHADS_2$ distribution (2/3/4–6), %	16/42/42
Index event (ischemic stroke/TIA), %	67/33
Clinical event rates	
AF detected at 90 d, 30-d ECG, %	16.1 (10.0–18.5)
AF detected at 90 d, 24-h repeat Holter, %	3.2 (1.5–6.0)
RR of intracranial hemorrhage (NOAC vs warfarin)	0.48 (0.40–0.55)
Odds ratio of intracranial hemorrhage (NOAC vs aspirin)	1.14 (1.00–2.00)
RR of overall major bleeding (NOAC vs warfarin)	0.86 (0.70–1.00)
RR of overall major bleeding (NOAC vs aspirin)	1.25 (1.00–1.50)

AF indicates atrial fibrillation; HR, hazard ratio; NOAC, new oral anticoagulants (apixaban, edoxaban, dabigatran, and rivaroxaban); RR, relative risk; SA, sensitivity analyses; and TIA, transient ischemic attack.

Canadian costs and converted the currency to US dollars using the rate of USD$1 to CAD$1.30. All costs were adjusted to 2014 dollars using the Consumer Price Index for health care.[38] We estimated QALYs by weighting length of life with the general population utility score and health state–specific utility weight (Methods section and Table II in the online-only Data Supplement).

Analyses

To assess cost-effectiveness, we calculated the incremental cost-effectiveness ratio, which is a ratio of incremental average costs between 2 strategies to the difference in their effect (QALYs). A strategy was considered highly cost-effective if it cost <$20 000 per QALY gained and low value if it cost ≥$100 000 per QALY gained.[39] One- and 2-way sensitivity analyses were conducted by varying model inputs over a plausible range (Table 1; Tables I and II in the online-only Data Supplement) to assess their effects on the results. To validate our model, we performed logic checks by reviewing the results of 1-way sensitivity analyses. Probabilistic sensitivity analysis was performed to characterize uncertainty by randomly sampling the model inputs 10 000× from the assigned distribution (Tables III and IV in the online-only Data Supplement). The estimated 10 000 pairs of incremental costs and QALYs were plotted to show the probability that a strategy was cost-effective at different willingness-to-pay thresholds (eg, $100 000 per QALY gained).

Results

Base Case Analysis

A strategy of 30-day ECG monitoring detected 129 more cases of AF and led to 104 more subclinical AF patients receiving anticoagulant therapy, for every 1000 patients screened. Our model predicted that 16 more ischemic strokes would be prevented at the expense of 2 more intracranial hemorrhages during a lifetime, for every 1000 patients screened. Overall, 30-day ECG monitoring was highly cost-effective (incremental cost-effectiveness ratio: $2000 per QALY gained); it was predicted to gain 17 life-years and 13 QALYs at an additional cost of $28 000 in a cohort of 1000 patients (Table 2).

In secondary analyses evaluating shorter monitoring durations, which lowered the AF detection rates and cost of monitoring, both 7- and 14-day monitoring were cost saving and clinically effective in preventing ischemic stroke when compared with a repeat 24-hour Holter (Table V in the online-only Data Supplement). Among the monitoring strategies, 30-day monitoring was the most clinically effective (estimated numbers needed to screen to prevent 1 ischemic stroke: 254, 102, and 63 for 7-, 14-, and 30-day monitoring, respectively).

Table 2. Results Comparing 30-Day ECG and Repeat 24-Hour Holter Monitoring, Base Case

	30-d ECG	Repeat 24-h Holter	Incremental
Ischemic stroke	0.195	0.211	−0.016
Intracranial hemorrhage	0.059	0.057	0.002
Major bleeding	0.233	0.227	0.007
Life-year	8.176	8.148	0.028
Life-year (discounted)*	6.137	6.119	0.017
QALY	5.857	5.837	0.020
QALY (discounted)*	4.467	4.454	0.013
Monitoring cost, $	447	131	316
Cost of ischemic stroke, $	17 604	18 960	−1356
Other costs, $	41 661	40 707	954
Total cost, $	59 712	59 798	−86
Total cost (discounted),$ *	43 689	43 661	28
Number needed to screen to prevent 1 ischemic stroke			63
Incremental cost per QALY gained (discounted),* $/QALY			2166

QALY indicates quality-adjusted life-years.
* Discounted at 5% per year.

Sensitivity Analyses

The incremental costs and QALY gained associated with 30-day monitoring from 1-way sensitivity analyses were plotted (Figure 1). Thirty-day monitoring was either cost saving or cost <$100 000 per QALY gained in all but one scenario; it cost $120 000 per QALY gained when we assumed anticoagulation reduced ischemic stroke risk by only 20%. In subgroup analyses, 30-day monitoring was highly cost-effective for younger (55 years) patients; it was cost saving and more effective in patients with higher risks of AF (≥80 years of age or those with frequent atrial ectopy[40]).

The 2-way sensitivity analysis results (Figure 2) show how cost-effectiveness changed across a range of assumptions for annual ischemic stroke risk and effectiveness of anticoagulation in preventing ischemic stroke. For example, 30-day monitoring, at a cost of $447, would be considered low value in patients with an ischemic stroke recurrence risk of 3% or lower if anticoagulation only reduced ischemic stroke risk by 30%. The results were more sensitive to these assumptions at higher monitoring costs. Cost-effectiveness of 7- and

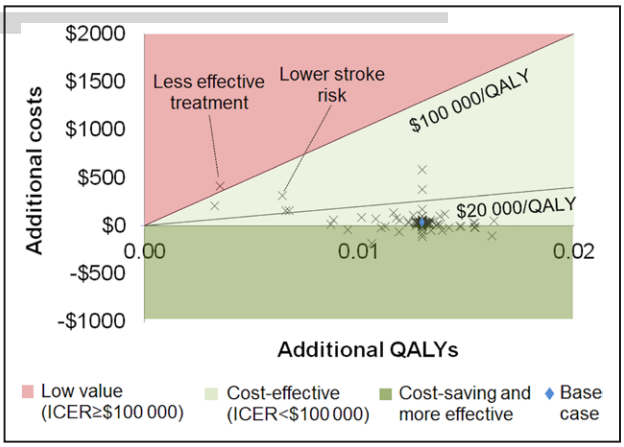

Figure 1. Results of 117 sensitivity analyses. Detailed results of scenarios that 30-day monitoring cost of ≥$20 000/QALY are listed in Table VI in the online-only Data Supplement. A strategy was considered highly cost-effective if it cost <$20 000/QALY and moderately cost-effective if it cost <$100 000/QALY.[39] ICER indicates incremental cost-effectiveness ratio, $/QALY gained. Less effective treatment: when the effectiveness of anticoagulant was reduced to 20% stroke risk reduction, 30-day monitoring cost $120 000 per quality-adjusted life-year (QALY) gained; lower stroke risk: in patients with stroke recurrence risk of 2.5% per year, 30-day monitoring cost $49 000 per QALY gained.

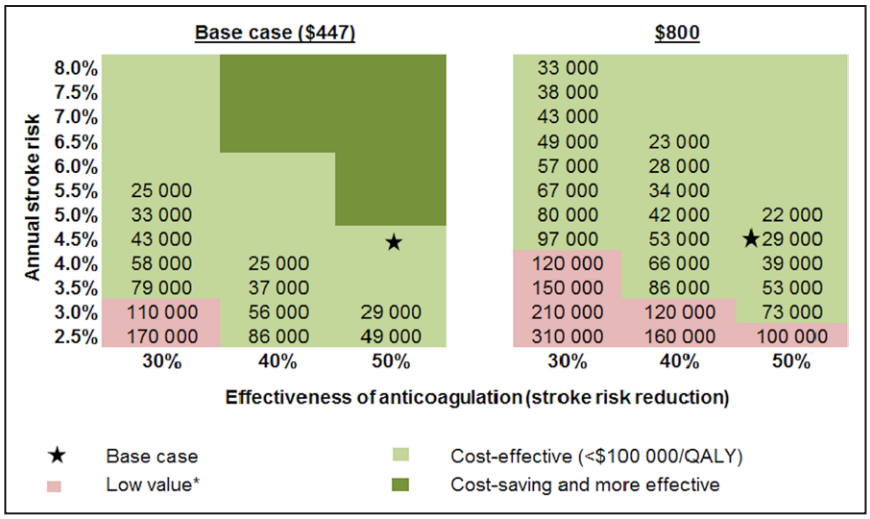

Figure 2. Results from 2-way sensitivity analyses varying ischemic stroke recurrence risk and effectiveness of anticoagulation at the same time when 30-day monitoring cost $447 (base case) and $800. Numbers on the table represent incremental cost-effectiveness ratios ($/QALY gained) for scenarios where 30-day monitoring cost $20 000 per quality-adjusted life-year (QALY) gained or more. *A strategy was considered low-value when it cost >$100 000/QALY.

14-day monitoring was less sensitive to changes in ischemic stroke risk and treatment effects (Figure II in the online-only Data Supplement). The probabilistic sensitivity analysis (Figure 3) shows that 30-day monitoring was more effective than repeat 24-hour monitoring 92% of the time. At a threshold of $100 000/QALY, 30-day monitoring was cost-effective 81% of the time when monitoring cost $447 (Figure III in the online-only Data Supplement) and 76% of the time when monitoring cost $800.

Discussion

Our findings suggest that noninvasive ECG monitoring for a target of 30 days is likely cost-effective among patients with a recent cryptogenic stroke or TIA. The results were sensitive to ischemic stroke risk and treatment benefit, especially at greater monitoring durations and costs.

This study is the first cost-effectiveness analysis of noninvasive monitoring for AF detection after cryptogenic stroke that uses effectiveness data from a randomized controlled trial, which minimizes the selection bias and confounding commonly present in observational studies. Our findings are consistent with previous cost-effectiveness analyses assessing outpatient poststroke ECG monitoring that used detection rates from observational studies.[41,42] One study found that 30-day intermittent ECG monitoring was cost saving and more effective than usual care in Sweden.[42] Another study found that 7-day monitoring cost $13 000 per QALY gained in the United States.[41] Their incremental cost was higher, partly because they assumed all patients with AF detected received β-blockers, and they were comparing their intervention to a strategy that had no cost of monitoring.

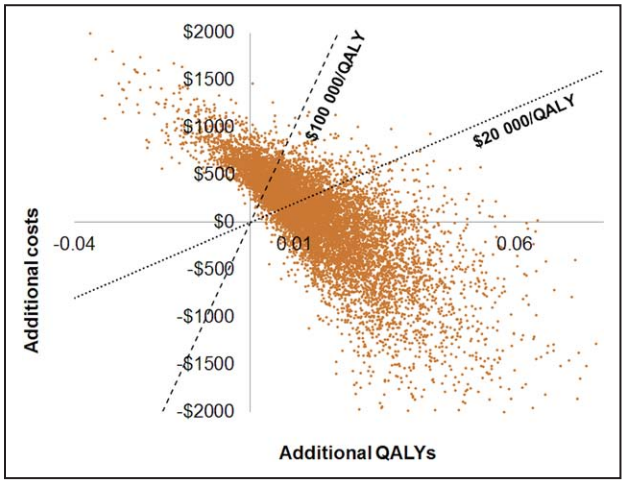

Figure 3. Plot of 10 000 pairs of incremental costs and quality-adjusted life-years (QALYs) from probabilistic sensitivity analysis.

This study has limitations. First, the results are predicted from a decision analytic model rather than observed events. Second, the risk of recurrent ischemic stroke associated with low-burden subclinical paroxysmal AF in patients with cryptogenic stroke is uncertain.[15] We acknowledge that the minimum duration of clinically significant AF remains controversial. In EMBRACE, the monitoring devices were limited to recording up to a maximum of 2.5 minutes of AF; >60% of the AF episodes detected lasted at least 2.5 minutes. If we assume that only patients with ≥2.5 minutes AF detected had an annual stroke recurrence risk of 4.5%, then the overall annual stroke risk would be 3.5%; 30-day monitoring would be considered low-value if anticoagulant therapy reduced ischemic stroke risk by <30% (apixaban reduced recurrent ischemic stroke rate by 71%).[18] The untreated annual stroke recurrence risk is highly unlikely to be lower than 3.5% because the average annual stroke risk is ≈3% to 8% in studies of patients with cryptogenic stroke (without documented AF), and the risk seems higher in patients with AF detected versus those without AF detected.[1,14,20] Third, the effectiveness of anticoagulation in this population is uncertain.[43] Currently available, but limited, evidence suggests that the relative risk reduction with anticoagulation is likely similar across different patterns of AF.[1,44] In two randomized trials of AF detection in stroke patients, fewer patients who received prolonged monitoring had recurrent stroke or TIA; however, these trials were not powered for that end point.[45] Trials underway will better inform us about this estimate.[46] To address the concerns of both limitations, our 2-way sensitivity analysis results show the potential cost-effectiveness over a wide range of effectiveness estimates. In addition, our effectiveness estimate in the base case was more conservative than in similar cost-effectiveness analyses.[41,42]

Our findings have implications for clinicians and policymakers. Cryptogenic stroke is common in everyday stroke practice. With practice guidelines now starting to recommend longer than 24 hours of ECG monitoring to detect AF after cryptogenic stroke,[5–7] our results support the recommendation that wearable devices enabling ≤30 days of monitoring be made available to the target population. Among the assessed strategies, 30-day monitoring was the most clinically effective, but 14-day monitoring can be an attractive alternative to policymakers. In EMBRACE, 75% of the AF cases were detected within the first 14 days of monitoring. Comparing 30-day versus 14-day monitoring, 30-day monitoring cost $28 000 per QALY gained, and there was less uncertainty around the cost-effectiveness of 14 days when the key assumptions (stroke risks and anticoagulant effectiveness) changed. In terms of generalizability, the AF detection rates were derived from an elderly and predominantly white Canadian secondary stroke prevention cohort who had nonlacunar, nonretinal, cryptogenic stroke events diagnosed by a stroke neurologist. The EMBRACE patients had mostly nondisabling strokes, and we assumed that they have long survival poststroke (8 years). Cost-effectiveness of monitoring in practice will depend on careful patient selection (especially given the tendency for overdiagnosis of TIAs), patients' functional status and life expectancy, and adherence with monitoring and treatment.

Summary

After a recent cryptogenic stroke or TIA, 30-day ECG monitoring is likely highly cost-effective for preventing recurrent strokes. A 14-day ECG protocol provides an attractive value alternative, especially for lower risk patients, as it seems cost saving and more effective than a repeat 24-hour ECG. These results lend support to emerging practice guidelines recommending longer (≥7 days) poststroke ECG monitoring in carefully selected patients to optimize secondary stroke prevention. At greater monitoring durations and costs, cost-effectiveness depends on the stroke recurrence risk and effectiveness of anticoagulation, which remain uncertain. Future trials that clarify the stroke risk associated with subclinical AF and the effectiveness of anticoagulant therapy in this population will further inform the cost-effectiveness of prolonged monitoring strategies.

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Disclosures

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