Atrial fibrillation (AF) is a common and treatable cause of ischemic stroke. AF causes approximately 15% of strokes, and treatment with anticoagulation reduces the annual risk of recurrent stroke in patients with AF by two thirds. Thus, it is important to determine whether patients who have had an ischemic stroke have underlying AF. However, AF is frequently paroxysmal and asymptomatic, making its diagnosis difficult. To address this, clinical guidelines recommend that patients with ischemic stroke undergo at least 24 hours of inpatient cardiac monitoring to detect underlying AF.

More prolonged outpatient cardiac monitoring, however, is not widely accepted despite studies suggesting that it increases the chance of detecting paroxysmal AF. Anticoagulation has been proven to reduce the risk of recurrent stroke in patients with AF, and it follows that the detection and appropriate treatment of more cases of paroxysmal AF through the use of more prolonged cardiac monitoring will lead to better clinical outcomes. On the other hand, monitoring patients with stroke for >24 hours incurs additional cost and inconvenience, and its cost-effectiveness is unknown. We therefore examined the cost-effectiveness of outpatient cardiac monitoring to detect AF after ischemic stroke.

Materials and Methods

Design
We calculated the cost per quality-adjusted life-year (QALY) gained by outpatient cardiac monitoring after ischemic stroke. As detailed subsequently, we used meta-analysis to obtain key model inputs. We compared 2 strategies: (1) standard care, whereby aspirin is prescribed after ischemic stroke and no outpatient cardiac monitoring is performed; versus (2) an additional 7 days of outpatient cardiac monitoring, which could detect AF and trigger a change from aspirin to warfarin.

Analysis
Because the yield of outpatient cardiac monitoring after ischemic stroke was a key input in our model, we estimated this parameter using a systematic review of the English-language literature. We used broad, standardized criteria (Table 1) to search all studies published between 1966 and 2008 and listed in the MEDLINE database. One investigator (H.K.) reviewed all abstracts identified in this manner and excluded studies that were obviously irrelevant. Two investigators (M.H. and D.J.) blinded to the study author(s) and journal independently reviewed the remaining studies and selected...
those that fulfilled prespecified inclusion criteria. Data were extracted using standardized forms. Disagreements were resolved by a third investigator (H.K.). The searches were complemented by reviewing the reference lists of all included publications and by using the “Related Articles” function on PubMed. Study authors were contacted for necessary clarifications and to inquire about unpublished data or studies. Four studies of the yield of outpatient cardiac monitoring in patients without AF after 24 hours of monitoring fulfilled our inclusion criteria. Schuchert et al studied patients for an additional 2 days and found new AF in 4.9% of patients; Barthelemy et al monitored for an additional 3 days and found new AF in 7.7% of patients; and Jaboub and et al monitored for an additional 7 days and found new AF in 5.7% of patients.7 Tayal et al monitored for an additional 21 days and found new AF in 23% of patients, but only 5.4% had episodes long enough to meet the standard definition of paroxysmal AF (ie, lasting >30 seconds).10,12 Using a random-effects model based on the method of DerSimonian and Laird,13 we performed a meta-analysis of these studies to estimate the yield of outpatient monitoring. All analyses were performed on the logit of the reported data to avoid compression of the standard error that can occur when the observed proportions are near zero.14 We tested for significant heterogeneity between studies using the Cochran Q test as well as the I2 method of Higgins and Thompson.15,16 Based on this analysis, we estimated that the yield of outpatient monitoring would be 5.9% (95% CI, 3.6% to 9.3%).

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To compare the cost and utility of warfarin and aspirin therapies to each group as calculated subsequently.

Table 1. Search Strategy and Inclusion Criteria of Literature Search for Yield of Outpatient Cardiac Monitoring to Detect AF After Ischemic Stroke

<table>
<thead>
<tr>
<th>Search Strategy</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>(“Electrocardiography, Ambulatory” OR ambulatory ECG OR EKG OR Holter OR “cardiac monitoring” OR telemetry OR “loop recorder”)</td>
<td>Consecutive patients with ischemic stroke</td>
</tr>
<tr>
<td>AND (“Atrial Fibrillation” OR “atrial flutter” OR “atrial fibrillation” OR flutter)</td>
<td>More than 24 hours of continuous cardiac monitoring Specifically report AF as an outcome</td>
</tr>
<tr>
<td>AND (“Stroke” OR stroke OR CVA OR “transient ischemic attack” OR “cerebral infarction” OR “cerebrovascular accident”)</td>
<td>Either exclude or state proportion of patients with known history of AF, AF on baseline electrocardiogram, and AF on &lt;24 hours of monitoring</td>
</tr>
</tbody>
</table>

Table 2. Value and Source of Key Model Inputs Used in the Base Case and Ranges Used in Sensitivity Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70</td>
<td>65–90</td>
<td>Assumed</td>
</tr>
<tr>
<td>Male, %</td>
<td>50</td>
<td>50</td>
<td>Assumed</td>
</tr>
<tr>
<td>Rate of ischemic stroke on aspirin, % per year</td>
<td>4.5</td>
<td>2–12</td>
<td>18</td>
</tr>
<tr>
<td>Relative risk of stroke, warfarin versus aspirin</td>
<td>0.48</td>
<td>0.37–0.63</td>
<td>18</td>
</tr>
<tr>
<td>Rate of hemorrhagic stroke on warfarin, % per year</td>
<td>0.4</td>
<td>0.4–1.2</td>
<td>18</td>
</tr>
<tr>
<td>Rate of major hemorrhage on warfarin, % per year</td>
<td>2.5</td>
<td>2.0–4.0</td>
<td>18</td>
</tr>
<tr>
<td>Relative risk of hemorrhage, aspirin versus warfarin</td>
<td>0.59</td>
<td>0.5–0.7</td>
<td>18</td>
</tr>
<tr>
<td>Utility of each life-year on warfarin</td>
<td>0.987</td>
<td>0.953–1.0</td>
<td>18</td>
</tr>
<tr>
<td>Utility of each life-year on aspirin</td>
<td>0.998</td>
<td>0.994–1.0</td>
<td>18</td>
</tr>
<tr>
<td>Utility of each life-year given major residual symptoms</td>
<td>0.39</td>
<td>0–1.0</td>
<td>18</td>
</tr>
<tr>
<td>Utility of each life-year given minor residual symptoms</td>
<td>0.75</td>
<td>0–1.0</td>
<td>18</td>
</tr>
<tr>
<td>Yield of outpatient cardiac telemetry to detect AF, %</td>
<td>5.9</td>
<td>0–20</td>
<td>7–10</td>
</tr>
<tr>
<td>Rate of diagnosis of AF without outpatient monitoring</td>
<td>25</td>
<td>0–95</td>
<td>17</td>
</tr>
<tr>
<td>Rate of incidental arrhythmias requiring evaluation, %</td>
<td>5</td>
<td>0–20</td>
<td>10, 24, 25</td>
</tr>
<tr>
<td>Cost of outpatient monitoring, $</td>
<td>168</td>
<td>50–2500</td>
<td>23, 52, 53</td>
</tr>
<tr>
<td>Rate of β-blocker use, %</td>
<td>100</td>
<td>0–100</td>
<td>12, 21, 33</td>
</tr>
<tr>
<td>Rate of cardioversion or ablation, %</td>
<td>0</td>
<td>0–50</td>
<td>12, 21, 33</td>
</tr>
<tr>
<td>Rate of pacemaker placement, %</td>
<td>0</td>
<td>0–5</td>
<td>10, 24, 25</td>
</tr>
<tr>
<td>Rate of electrophysiological study, %</td>
<td>0</td>
<td>0–3</td>
<td>34–38</td>
</tr>
<tr>
<td>Rate of depression, %</td>
<td>0</td>
<td>0–2.5</td>
<td>39–41</td>
</tr>
<tr>
<td>Utility of remaining life-years with arrhythmia</td>
<td>1.0</td>
<td>0.99–1.0</td>
<td>39–41</td>
</tr>
</tbody>
</table>

*Further details about the variables used to calculate the cost and utility of warfarin versus aspirin in this model have been published previously.18
cardioversion or ablation and would instead be prescribed lifelong generic β-blockers to control their heart rate. The estimated cost of therapy for heart-rate control, based on the average annual wholesale cost of generic metoprolol at a dose of 50 mg twice daily, would be $403 per year. We estimated that 1 week of outpatient monitoring (with an event-triggered loop recorder) would cost $108, including the cost of equipment, technician services, and physician interpretation. We assumed that monitoring would incidentally reveal potentially serious cardiac arrhythmias other than AF in 5% of patients necessitating a cardiac evaluation. The estimated cost of this evaluation, based on the Medicare payment for a moderate-complexity outpatient consultation (Current Procedural Terminology code 99244), would be $150. We did not include the cost of echocardiography because it is routinely included in the evaluation of patients with stroke.

We calculated costs from the perspective of a health maintenance organization or insurance company paying for medical care and prescription drugs. Lost wages are small in this population and were captured in the utilities used for the various health states. Our analysis was identical to 1 taking a societal perspective, except for the exclusion of costs borne by caretakers. We did not calculate the direct effect of outpatient cardiac monitoring on patients’ quality of life because it is well tolerated and the duration of monitoring is relatively short; however, the potential long-term effects on quality of life of a diagnosis of AF or an incidentally discovered arrhythmia were explored in sensitivity analyses. Costs and life-years were discounted at 3%. Costs and utilities were projected over a maximum of 20 years; median expected survival was 13.3 years. Costs were converted to 2010 dollars using the medical care component of the consumer price index. We defined cost-effective as a cost-utility ratio of $50 000 per QALY. To examine the effects of our assumptions and model inputs on the cost-utility ratio, we performed univariate sensitivity analyses by changing each input at the same time as holding other variables constant, as described in detail subsequently.

Sensitivity Analysis

We performed sensitivity analyses to examine our assumptions about the natural history of undiagnosed AF. Monitoring may (1) reveal AF that would never have been diagnosed; (2) reveal AF that would eventually have been diagnosed by other means; (3) truly rule out AF; (4) fail to reveal AF that then remains undiagnosed; and (5) fail to reveal AF that is eventually diagnosed by other means. Our base case assumed a mix of scenarios 1, 2, and 3, and we examined the effects of our chosen inputs by varying the relative proportions of these scenarios (ie, by varying the yield of outpatient monitoring and the proportion of patients whose AF would be diagnosed by other means before a recurrent stroke). Scenarios 4 and 5 had no effect on quality-adjusted survival in our model, because in these cases, the natural history of AF would be unaffected by outpatient monitoring; the effect on cost was addressed by varying the yield of outpatient monitoring.

To examine the effect of inputs used to calculate the cost and utility of warfarin therapy for stroke prevention, we varied the key parameters in our model across a wide range. We examined the cost implications of differing strategies for managing AF by varying the proportion of patients who would receive a trial of cardioversion in addition to rate-control agents. Guidelines recommend against cardioversion for patients in our study population, but it continues to be used in the community, albeit at a decreasing rate. In addition, we varied the proportion of patients who would undergo catheter ablation for AF, although this procedure is indicated in patients with symptomatic AF. To test our assumption that patients with incidentally discovered arrhythmias would require only cardiac consultation, we varied the proportion of patients for whom outpatient monitoring would lead to further interventions such as pacemaker placement or invasive electrophysiological testing. Based on studies of cardiac monitoring after stroke, we estimated a priori that monitoring might directly lead to pacemaker placement in at most 5% of patients. Furthermore, outpatient monitoring might directly lead to placement of an automatic implantable cardioverter–defibrillator (AICD) if it were to reveal nonsustained ventricular tachycardia in an asymptomatic patient with prior myocardial infarction and a left ventricular ejection fraction of 30% to 40%. For these patients to qualify for an AICD, invasive electrophysiological study must show inducible ventricular fibrillation or sustained ventricular tachycardia, which might be found in approximately one third of these patients. In our base case, we assumed that a negligible proportion of patients would fit this narrow and specific profile, but we varied the proportion in our sensitivity analyses. Using studies of cardiac monitoring after stroke, the prevalence of congestive heart failure in patients with stroke, and studies of echocardiography after stroke, we estimated a priori that at most 3% of patients might undergo an invasive electrophysiological study to evaluate the need for an AICD. We also performed a separate sensitivity analysis taking into account the QALYs gained from AICD placement.

Lastly, the discovery of AF and other arrhythmias may affect the cost-effectiveness of outpatient monitoring by decreasing patients’ quality of life. We explored this in our sensitivity analyses by examining the effects of major depression (with a reduction of 0.2 in the utility of patients’ remaining life-years) in a plausible proportion of patients discovered to have AF or another arrhythmia. We also examined this from a slightly different perspective by assuming a small decrease in the value of the remaining life-years of all patients with AF or another arrhythmia. Given the relatively small increases in symptoms of depression and anxiety or absenteeism from work found in studies of screening for asymptomatic conditions, we estimated a priori that at most 2.5% of patients diagnosed with AF or another arrhythmia might develop depression because of the new diagnosis, or that the utility of the remaining life-years of all patients with AF or another arrhythmia might be reduced by at most 1%.

Results

Cost-Utility

In a 70-year-old patient with nonvalvular AF and prior ischemic stroke, lifelong warfarin therapy would result in a gain of 0.782 QALYs and would cost $1627 more than aspirin (this includes the higher cost of warfarin therapy versus the cost savings from fewer strokes compared with aspirin). Outpatient cardiac monitoring would detect 59 new cases of AF for every 1000 patients monitored compared with 15 new cases that would be diagnosed per 1000 patients without monitoring and by triggering warfarin therapy would result in a comparative gain of 34 QALYs. The cost of monitoring 1000 patients would be $168 000; the cost of β-blocker therapy and the comparative cost of warfarin in those identified to have AF would be $264 000; and the cost of cardiological consultation in those with an incidentally discovered arrhythmia other than AF would be $7500, resulting in a net cost of approximately $440 000. Therefore, the cost-utility ratio of outpatient cardiac monitoring would be approximately $13 000 per QALY gained (Table 3).

Sensitivity Analysis

The cost-utility ratio of outpatient monitoring was plotted for a range of values of key model inputs (Figure). Monitoring was cost-effective at any yield >0.8% and any cost <$2000 per patient. In addition, outpatient monitoring remained cost-effective even if up to 85% of patients with underlying AF were to be diagnosed without outpatient monitoring and started on warfarin before a recurrent stroke; in other words, even if only 15% of those with underlying AF were to remain...
undianagnosed until presenting with another stroke, the QALYs that would have been saved by expeditiously diagnosing that small group of patients would justify the expense of routine outpatient monitoring. Lastly, outpatient monitoring after stroke remained cost-effective even if it were to lead to the maximum reasonable proportion of patients undergoing additional interventions such as electrophysiological study or pacemaker or AICD placement.

Discussion

In this cost-utility analysis based on a systematic review of the literature, 1 week of continuous outpatient cardiac monitoring after ischemic stroke appears cost-effective through identification of patients with underlying paroxysmal AF who would benefit from warfarin therapy. Outpatient monitoring would be expected to establish a new diagnosis of AF in 4.4% of patients at an approximate cost of $13 000 per QALY gained, well below a standard $50 000 per QALY threshold generally considered cost-effective.30

When determining the utility of warfarin versus antiplatelet therapy in patients with AF and stroke, we chose aspirin as the standard antiplatelet agent for several reasons. First, we could not find any randomized trials comparing warfarin with clopidogrel or low-dose aspirin plus extended-release dipyridamole for the prevention of recurrent stroke in patients with AF. A recent trial compared warfarin with the combination of aspirin and clopidogrel,42 but in our base case, patients with undiagnosed AF would be treated with a single antiplatelet agent per the standard of care.20 Second, although clopidogrel and low-dose aspirin plus extended-release dipyridamole may be slightly superior to aspirin for secondary stroke prevention, a recent analysis showed this difference to be slight43 and probably not of significance to our model. In estimating the annual risk of stroke with aspirin in our patient population, we initially looked to 2 randomized trials comparing warfarin with aspirin for the prevention of recurrent stroke in patients with AF.44,45 However, in this era of aggressive statin use46 and blood pressure control,47 the annual rate of recurrent stroke on aspirin in patients with AF is probably lower than the 9% to 10% rate seen in these 2 studies.44,45 In a recent trial, patients with AF and a history of stroke or transient ischemic attack who were not eligible for warfarin had a 6.3% annual rate of recurrent stroke while taking aspirin.48 To be conservative, we estimated a 4.5% annual risk of recurrent stroke with aspirin. It is notable that even as aggressive lipid and blood pressure control has led to lower overall rates of recurrent stroke in patients with AF, warfarin remains superior to antiplatelet therapy for the prevention of recurrent stroke,42 and therefore our assumptions about the efficacy of warfarin remain applicable. Furthermore, although there are many promising new treatments for stroke prevention in AF such as the direct thrombin inhibitor

Table 3. Costs and Quality-Adjusted Survival Associated With Outpatient Cardiac Monitoring in the Base Case, Which is a Hypothetical Cohort of 70-Year-Old Patients With AF, Prior Stroke, and No Contraindication to Warfarin Therapy

<table>
<thead>
<tr>
<th>No. of hypothetical patients</th>
<th>Outpatient Monitoring</th>
<th>Standard Care</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime cost associated with warfarin,* $</td>
<td>95 000</td>
<td>24 000</td>
<td>71 000</td>
</tr>
<tr>
<td>Lifetime cost of β-blockers, $</td>
<td>257 000</td>
<td>64 000</td>
<td>193 000</td>
</tr>
<tr>
<td>Cost of cardiological evaluation, $</td>
<td>7500</td>
<td>0</td>
<td>7500</td>
</tr>
<tr>
<td>Cost of monitoring, $</td>
<td>168 000</td>
<td>0</td>
<td>168 000</td>
</tr>
<tr>
<td>Net cost, $</td>
<td>528 000</td>
<td>88 000</td>
<td>440 000</td>
</tr>
<tr>
<td>Increase in QALYs</td>
<td>46</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>Cost-utility ratio ($/QALY)</td>
<td>13 000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This is the net cost of warfarin therapy compared to aspirin therapy, which reflects the higher cost of warfarin as well as the cost savings from prevention of strokes compared with aspirin.

Figure. Univariate sensitivity analyses of the cost-utility ratio of outpatient cardiac monitoring as a function of key variables. Base case values of model inputs are shown in Table 2.
dabigatran and devices for percutaneous closure of the left atrial appendage, these treatments have not been widely proven and adopted in clinical practice, and for now, warfarin remains the gold standard for the prevention of thromboembolism in patients with AF.

To examine the effect of age on the cost-effectiveness of outpatient cardiac monitoring, we varied the age of patients in our model from 65 to 90 years. Assuming a constant rate of stroke throughout this age range, outpatient cardiac monitoring was more cost-effective in younger patients, probably because of the greater cumulative risk of stroke in younger patients with AF and the higher long-term costs of caring for younger stroke survivors. However, this analysis did not account for the fact that younger patients with AF face a lower yearly risk of stroke than older patients. Furthermore, it is important to emphasize that our sensitivity analyses did not extend to patients <65 years of age, and so our results cannot be extrapolated to young patients with stroke for whom many of the parameters we assumed in our model may not be applicable.

In selecting cost inputs for our base case, we used the cost of 1 week of monitoring, because there are few data on the yield of longer periods of monitoring. However, outpatient cardiac event monitors are commonly reimbursed on a 30-day basis. The cost of 30 days of outpatient cardiac monitoring ranges from $284 to $783 with an average of $532. As seen in our sensitivity analyses, outpatient monitoring remained cost-effective throughout this range, even without assuming an increased yield from a longer period of monitoring. We based our model on the use of autotriggered, nonattended, surface loop recorders as the most economical and rational choice for monitoring. A wide variety of devices and services are available to provide outpatient ambulatory electrocardiography; choices include implantable versus surface electrodes, the real-time availability of a technician or physician to review recordings, patient- versus autotriggered recording, and automatic versus manual data transmission. Patient-triggered event monitors are unlikely to detect asymptomatic AF. Furthermore, although the detection of AF in a patient with a recent stroke should lead to prompt consideration of anticoagulation therapy, it is not a medical emergency requiring 24-hour technician or physician review. The study that we used to estimate the cost of cardiac monitoring did not specify whether the monitors used were patient- or event-triggered, but these types of monitors have similar costs and reimbursement.

In estimating the utility of outpatient cardiac monitoring, we assumed that underlying paroxysmal AF not diagnosed at the time of stroke would eventually be diagnosed before a recurrent stroke in one fourth of cases. This assumption was based on preliminary findings from a study examining the rate of new diagnoses of AF after ischemic stroke; regardless, our cost-utility ratio was relatively insensitive to changes in this proportion. Furthermore, our model assumed a flat rate of stroke recurrence, but the risk of recurrent stroke in patients with AF is probably higher in the short term; a recent meta-analysis of randomized trials of anticoagulation for acute cardioembolic stroke showed a 4.9% rate of recurrent stroke within 2 weeks. Although outpatient monitoring would not lead to treatment of AF within the first few weeks, both for practical reasons (ie, the time required to arrange and obtain results from monitoring and then achieve therapeutic levels of anticoagulation) and safety reasons (ie, the increased risk of hemorrhage seen with acute anticoagulation for stroke from AF), the asymptotic nature of the rate of recurrent stroke may increase the importance of rapidly diagnosing AF. This would partially offset the fact that patients with underlying AF may eventually be diagnosed in the long term without monitoring. In addition, in our base case, we assumed that all patients with ischemic stroke would be monitored, but monitoring only patients with unexplained or suspected cardioembolic stroke may increase the yield of monitoring. In a recent study, 30 days of outpatient monitoring revealed previously undiagnosed AF in 20% of selected patients with cryptogenic stroke. When including the study by Tayal et al in our meta-analysis, we conservatively included only episodes of AF lasting >30 seconds, but these investigators found briefer episodes of AF in 23% of patients with cryptogenic stroke.

Monitoring in this population aims to detect cases of asymptomatic AF, and so we did not include in our base case the costs of cardioversion or ablation, because these procedures are indicated in selected patients with symptomatic AF, which would come to light even without monitoring. We further assumed that all patients with a potentially serious arrhythmia other than AF would simply be referred to a cardiologist for evaluation. However, it is possible that some patients would undergo cardioversion or ablation or receive more extensive investigation of incidental arrhythmias, thereby decreasing the cost-effectiveness of outpatient cardiac monitoring. Regardless, in our sensitivity analyses, outpatient cardiac monitoring remained cost-effective if the maximum reasonable proportion of patients underwent cardioversion, ablation, electrophysiological testing, or pacemaker or AICD placement, even without considering any QALYs gained from these procedures.

In addition to the cost implications of incidental findings as discussed, we also examined their effect on patients’ quality of life. Studies have suggested that the incidental discovery of medical conditions may increase anxiety, depressive symptoms, and absenteeism from work; the discovery of AF or other asymptomatic arrhythmias by outpatient monitoring may have similar adverse effects. However, the effect on quality of life in these studies was clinically small. Furthermore, it may not be appropriate to directly compare the reduction in disability and the years of life saved by detection of AF with a reduction in patients’ quality of life from incidentally discovered asymptomatic conditions that do not affect patients’ lifespans. In any case, varying the utility of the remaining life-years of patients with incidentally discovered arrhythmias throughout a reasonable range did not significantly change our final cost-utility ratio.

Lastly, cost-effectiveness analyses should preferably take a societal perspective and, strictly speaking, ours did not because we excluded the costs of caretakers. However, because monitoring would be expected to reduce the rate of recurrent stroke and therefore the need for caretakers, includ-
ing these costs would probably have increased the cost-effectiveness of outpatient cardiac monitoring.

Summary

Our analysis suggests that 1 week of outpatient cardiac monitoring after ischemic stroke is cost-effective. Guidelines published by the American Heart Association and the American Stroke Association in 2006 recommend that patients with acute ischemic stroke undergo cardiac monitoring to detect important cardiac arrhythmias, including AF. They note the absence of clinical trials addressing the optimal length of monitoring and report a general consensus that monitoring should extend for at least 24 hours. Multiple studies have shown that monitoring beyond 24 hours detects more cases of AF, but objections to outpatient cardiac monitoring have been raised because of a perceived lack of cost-effectiveness. Therefore, our study may justify changing the guidelines so that routine outpatient cardiac monitoring is recommended. Our analysis would be made more robust by more data on the yield of outpatient cardiac monitoring, but even with existing data, we recommend at least 1 week of outpatient cardiac monitoring to detect underlying AF in patients with unexplained stroke.

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Disclosures

None.

References


Cost-Effectiveness of Outpatient Cardiac Monitoring to Detect Atrial Fibrillation After Ischemic Stroke

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缺血性卒中后门诊心脏监测发现心房颤动的成本效益分析
Cost-Effectiveness of Outpatient Cardiac Monitoring to Detect Atrial Fibrillation After Ischemic Stroke
Hooman Kamel, MD; Manu Hegde, MD, PhD; Derek R. Johnson, MD; Brian F. Gage, MD, MSc S. Claiborne Johnston, MD, PhD

背景和目的：心房颤动（AF）是卒中一个重要的可治疗病因，延长缺血性卒中后连续心电监测的时间能够发现更多的AF病例，但这种方法的成本效益比尚不清楚。因此，我们进行了缺血性卒中后门诊心脏监测成本效益研究。

方法：利用Markov模型，我们确定了一个假设队列，这个队列由一些70岁有卒中史、伴AF、没有华法林禁忌症的患者组成，我们研究了使用华法林治疗的终生的成本效益比，并使用Meta分析评价了门诊心脏监测的收益。

结果：门诊每进行1000个心脏监测将发现44例新的AF患者。以440,000美元的净成本能获得34个质量调整生命年（QALY）。因此，心脏监测费用的成本效益比为13,000美元/QALY。在敏感性分析中，在一个较大的模型输入量范围内，门诊心电监测都有较好的成本效益比，包括监测成本和收益的改变。

结论：通过门诊心脏监测发现的阵发性AF患者将从抗凝治疗中获益，进行缺血性卒中后心脏监测在一个较大的模型成本投入范围内都有较好的成本效益比，但监测的最佳周期和方法尚不清楚。

关键词：心房颤动，心律失常，心源性栓子，心源性栓塞，成本效益分析，诊断方法，心电图，脑栓塞

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监测未发现 AF 的患者进行门诊心电监测的研究符合我们的纳入标准。Schuchert 等在 24 小时后额外为患者进行了 2 天的心电监测, 发现了 4.9% 的患者有新的 AF 发生[9]。Barthelemy 额外监测了患者 3 天, 发现了 7.7% 的患者有新的 AF 发生。Jabaudon 等额外监测了患者 7 天, 发现了 5.7% 的患者有新的 AF 发生[7]。Tayal 等额外监测了患者 21 天, 发现了 23% 的患者有新的 AF 发生, 但只有 5.4% 的患者发作期足够长, 能够满足阵发性 AF 定义的标准 (即持续超过 30 秒) [10,11]。使用基于 DerSimonian and Laird 方法的随机效益模型[13], 我们对相关研究进行了 meta 分析, 估计了门诊心电监测的效益。所有的研究数据均采用对数形式, 以免数据接近 0 时对标准误可能产生的影响 [14], 用 Cochran Q 检验以及 Higgins 和 Thompson 的 I² 方法 [15,16] 来检验各研究之间的异质性。通过分析, 我们估计门诊心脏监测的效益是 5.9%(95% CI, 3.6%-9.3%)。四个试验之间无明显异质性差异 (Q 检验 P = 0.78; I² = 0)。

表 1 搜索缺血性卒中后门诊心脏监测发现 AF 的收益的文献——搜索策略和纳入标准

<table>
<thead>
<tr>
<th>搜索策略</th>
<th>纳入标准</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&quot;Electrocardiography, Ambulatory&quot; OR &quot;Ambulatory Electrocardiography&quot; OR &quot;Ambulatory ECG&quot; OR &quot;Ambulatory EKG&quot; OR Holter OR &quot;cardiac monitoring&quot; OR telemetry OR &quot;loop recorder&quot;) AND (&quot;Atrial Fibrillation&quot; [Mesh] OR &quot;Atrial Flutter&quot; [Mesh] OR &quot;atrial fibrillation&quot; OR &quot;atrial flutter&quot;)</td>
<td>超过 24 小时的连续心电监测</td>
</tr>
<tr>
<td>(&quot;Stroke&quot; [Mesh] OR stroke OR &quot;transient ischemic attack&quot; OR &quot;cerebral infarction&quot;)</td>
<td>作为结果的特别报道的 AF</td>
</tr>
</tbody>
</table>

表 2 敏感性分析中, 在基础病例中使用的重要模型输入变量的值、范围以及来源 *

<table>
<thead>
<tr>
<th>变量</th>
<th>值</th>
<th>范围</th>
<th>参考文献</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄, 岁</td>
<td>70</td>
<td>65-90</td>
<td>假定</td>
</tr>
<tr>
<td>男性, %</td>
<td>50</td>
<td>50</td>
<td>假定</td>
</tr>
<tr>
<td>阿司匹林组缺血性卒中率, % 每年</td>
<td>4.9</td>
<td>2-12</td>
<td>18</td>
</tr>
<tr>
<td>华法林组出血性卒中率, % 每年</td>
<td>0.4</td>
<td>0.4-1.2</td>
<td>18</td>
</tr>
<tr>
<td>华法林组出血性卒中率, % 每年</td>
<td>2.5</td>
<td>2.0-4.0</td>
<td>18</td>
</tr>
<tr>
<td>华法林组出血性卒中率, % 每年</td>
<td>0.59</td>
<td>0.5-0.7</td>
<td>18</td>
</tr>
<tr>
<td>华法林组出血性卒中率, % 每年</td>
<td>0.987</td>
<td>0.953-1.0</td>
<td>18</td>
</tr>
<tr>
<td>华法林组出血性卒中率, % 每年</td>
<td>0.998</td>
<td>0.994-1.0</td>
<td>18</td>
</tr>
<tr>
<td>华法林组出血性卒中率, % 每年</td>
<td>0.39</td>
<td>0-1.0</td>
<td>18</td>
</tr>
<tr>
<td>华法林组出血性卒中率, % 每年</td>
<td>0.75</td>
<td>0-1.0</td>
<td>18</td>
</tr>
<tr>
<td>门诊心脏监测发现 AF 的益处</td>
<td>5.9</td>
<td>20</td>
<td>7-10</td>
</tr>
<tr>
<td>无监测诊断为 AF 的门诊患者, %</td>
<td>25</td>
<td>0-95</td>
<td>17</td>
</tr>
<tr>
<td>需要进一步评估的偶发心律失常, %</td>
<td>5</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>门诊监测花费, 美元</td>
<td>168</td>
<td>50-2500</td>
<td>23, 52, 53</td>
</tr>
<tr>
<td>β 阻断剂的应用率, %</td>
<td>100</td>
<td>0-100</td>
<td>12, 21, 33</td>
</tr>
<tr>
<td>心脏转复或消融术率, %</td>
<td>0</td>
<td>0-100</td>
<td>12, 21, 33</td>
</tr>
<tr>
<td>食管内电生理检查率, %</td>
<td>0</td>
<td>0-5</td>
<td>10, 24, 25, 34</td>
</tr>
<tr>
<td>β 阻断剂应用率, %</td>
<td>0</td>
<td>0-2.5</td>
<td>34-38</td>
</tr>
<tr>
<td>抑郁症发生率, %</td>
<td>0</td>
<td>0-3</td>
<td>39-41</td>
</tr>
<tr>
<td>伴心律失常的低生命年效用</td>
<td>1.0</td>
<td>0.99-1.0</td>
<td>39-41</td>
</tr>
</tbody>
</table>

从一种状态到另一状态的转变取决于之前的事件 (如, 一个卒中史的 AF 患者比一个单纯 AF 患者更容易发生卒中)。因此，我们使用了多种状态 (例如，单纯 AF，伴有卒中史的 AF，伴有颅内出血史的 AF 等)。我们的基础病例是一个由 70 岁的、有卒中史的、伴非瓣膜性 AF 的患者组成的队列。我们回顾了关于华法林治疗伴有 AF 的卒中患者的相关临床试验, 得到了下列重要的模型输入量：服用阿司匹林的患者平均卒中发生率为 4.5%, 服用华法林与服用阿司匹林相比, 发病率估计率为 0.48, 华法林治疗的出血性卒中年发生率估计为 0.4%, 服用阿司匹林与服用华法林相比, 出血性卒中的发病率为 0.59(表 2)[10,11]。在我们的模型中, 所有无 AF 的患者都接受华法林治疗后, 有 AF 的患者才需要进一步评估的偶发心律失常。
的美托洛尔计算,每年花在心率控制上的费用为 403 美元。我们估算门诊患者一周的心脏监测（包括事件触发循环记录）的费用为 168 美元，其中含器材、技术服务及医师咨询 [23]。我们假设通过监测发现 5% 的患者除 AF 之外的严重心律失常，需要进一步的心脏评估 [26-27]。这笔评估费用约为 150 美元（基于美国现有的医疗保险对中等复杂的门诊患者的诊疗费用支出） [26-27]。这不包括在病房心脏彩超的费用，因为常规上它包含在对卒中患者的评估中。

我们是从健康维护组织和为医疗护理和处方药付费的保险公司的角度来计算费用的。在这个人群中工资的损失很少 [28], 并被用于各种健康机构的公益事业。除了将看护者的费用负担排除之外，我们的分析是从社会负担的角度出发的。我们并没有计算门诊心脏监测对患者生活的质量产生的直接作用, 因为监测间期相对短, 易于耐受 [29]。但是, 我们对诊断出 AF 或是偶然发现的心律失常对长期的生活质量的潜在效益做了敏感性分析。成本与生命年数减少了 3% [30]。费用与效用最长持续时间为 20 年，预期中位生存期为 13.3 年。根据消费者价格指数 (CPI) 中的医疗费用, 成本被换算为 2010 年的美元水平 [31]。我们将有成本效益定义为成本收益比 ≤ 50 000 美元 / QALY [30]。为了检验我们的假设和各模型输入量对成本效益比的影响, 我们进行了单因素敏感性分析（改变一个输入量的同时保持其他变量恒定），以下将详述。

敏感性分析

我们进行了敏感性分析以检验对未诊断的 AF 患者自然史的假设。心脏监测可能: (1) 发现可能将始终不被诊断的 AF; (2) 发现可能将被其他方式诊断的 AF; (3) 确实排除 AF; (4) 未发现可能始终不被诊断的 AF; (5) 未发现可能将被其他方式诊断的 AF。我们假设了 1, 2, 3 混合在一起的情况，我们通过对改变三种情况的相对比例检验了各种输入量的效应。例如：改变心脏监测的收益，以及改变可能通过其他方法在卒中复发病诊断为 AF 的患者的比例。4, 5 两种情况对我们的质量调整生存没有影响，因为门诊心脏监测对这些患者的 AF 自然史没有影响；通过改变门诊心脏监测的收益来解决对成本的影响。

为了评估用来计算华法林预防卒中的花费和效益的输入量的影响，我们使模型中的关键参数在很大范围内变动。通过改变将要接受心脏复律联合心率控制药物治疗的患者的比率，我们检验了不同策略的费用。尽管指南不推荐在我们的实验人群中进行复律 [32], 但在社区中仍然在继续应用, 虽然比例在降低 [32]。此外，我们改变了将接受导管消融治疗的患者的比率，尽管这项操作仅推荐给症状性 AF 患者 [33]。

为了检验我们的假设——偶然发现心律失常的将只需要心脏病咨询, 我们改变那些经门诊心脏监测后需进行进一步干预措施 (例如心脏起搏器安置或有创电生理测试) 的患者比例。基于卒中后的心脏监测研究 [10,24,25], 我们预估心脏监测最多可能直接导致 5% 的患者安置起搏器 [44]。

此外, 若门诊监测到无症状的非持续性心动作过速、曾有心肌梗死病史且左心室射血分数为 30%-40% 的患者, 将会直接导致其安置自动的心脏除颤器 (AICD) [34]。放置 AICD 需要经过有创生理检查确认存在可诱导的心室颤动或持续性室性心动过速，大约三分之一患者属于这种情况 [35]。在我们的基础病例中，我们将这种特殊情况考虑，几乎可忽略不计 [36]。但我们的敏感性分析中，我们还是改变了这部分患者的比率 [36]。根据卒中后心脏监测研究 [10,24,25], 约半数卒中患者中充血性心衰的患病率 [20], 以及卒中后经食管心脏超声研究 [37,38], 我们预估最多 3% 的患者需要进行侵入性的电生理检查，以评价是否需要 AICD。我们也进行了把 AICD 植入对 QALYs 的影响考虑在内的独立的敏感性分析 [36]

最后，发现 AF 和其它心律失常也可降低患者的生活质量，从而影响门诊心脏监测的的成本效用。我们在敏感性分析中探讨了这一点——在一个比例合理的被发现患有 AF 或其它心律失常的患者中，评估严重抑郁（患者的剩余生命年减少 0.2 [39]）的影响。我们也从另一个稍有不同的角度进行了评估, 即假设所有患 AF 或其它心律失常的患者剩余生命年都会有一个幅度的减少。考虑到那些筛选无症状 AF 的研究所提示的抑郁和焦虑症状 [40] 以及旷工的现象仅轻度增加 [41], 我们预估最多 2.5% 的被诊断出 AF 或其它心律失常的患者由于疾病被诊断而发展为抑郁症，或者说所有患 AF 或其它心律失常的患者的剩余生命年最多会减少 1%。

结果

成本效用

对于一个 70 岁的、有缺血性卒中史、患非瓣膜性 AF 的患者，终生的华法林治疗将带来 0.782 QALYs，但是将比阿司匹林多花费 1627 美元 (包括
较高的华法林治疗花费，以及减去较少的卒中复发次数所节约的花费。门诊心脏监测能在 1000 例患者中发现 59 例新 AF 患者，相比而言，不进行监测只能发现 15 例。通过使这些患者转为华法林治疗，将带来 34 QALYs 的相对收益。监测 1000 名患者的花费为 168000 美金，被识别为 AF 的患者服用 β 受体阻断剂的费用以及华法林治疗的相对花费为 264000 美金，那些偶然发现除 AF 以外的心律失常的患者进行心脏病咨询的花费为 7500 美金，总净花费约为 440000 美金。因此门诊心脏监测的成本效益比约为每 QALY 13000 美金（表 3）。

敏感性分析

在一系列重要模型输入变量范围内我们绘制了门诊监测的成本效益比。每个患者任何收益 >0.8% 及任何花费 <2000 美金的情况下，门诊检测是有成本效益的。此外，即使 85% 的潜在性 AF 在没有进行门诊监测的情况下被诊断出来，并在卒中复发前开始华法林治疗，门诊检测仍然有成本效益。换而言之，即使只有 15% 的患者直到卒中复发后才能得到诊断，这一小部分人因迅速得到诊断所节省的 QALYs 将证实常规门诊监测的花费是合理的。最后，即使卒中后门诊心脏监测将导致最大可能比例的患者进行额外的干预措施，如电生理检查、起搏器或 AICD 植入，它仍然具有成本效益。

讨论

这项基于系统性回顾的成本效用研究中，缺血性卒中后连续一周的心脏门诊监测有成本效用，因为它可识别出潜在的阵发性 AF 患者，而这些患者将在华法林治疗中获益。门诊心脏监测被期望能够诊断 4.4% 的新 AF 患者，其成本约为每获得 1 个 QALY 花费 13000 美金，远低于一般认为的成本有效指标上限，即每获得 1 个 QALY 花费 50000 美金。

在判定那些有卒中史的 AF 患者服用华法林还是阿司匹林更有效的时候，我们因为以下几个原因选择了阿司匹林作为标准的抗血小板制剂：第一，在对于 AF 患者的卒中二级预防，我们未找到任何随机试验比较华法林和氯吡格雷，或华法林和小剂量阿司匹林加长效双嘧达莫。一个最近的研究比较了华法林和联合应用阿司匹林加氯吡格雷[42]，但在我们的基础病例中，按照标准化治疗，未诊断 AF 的患者只接受单一抗血小板治疗[20]；第二，尽管对

<table>
<thead>
<tr>
<th>监测的收益，%</th>
<th>监测的成本，美金</th>
<th>年龄，岁</th>
<th>有 AF 的患者服用阿司匹林的卒中发生率，%</th>
<th>华法林的出血率，%</th>
<th>不进行监测发现 AF 的比率，%</th>
<th>偶发的心律失常发生率，%</th>
<th>β 阻断剂的应用率，%</th>
<th>心脏转复的比例，%</th>
<th>起搏器植入率，%</th>
<th>电生理检查的比例，%</th>
<th>电生理检查的比率 *，%</th>
<th>抑郁症的比例，%</th>
<th>剩余生命年的效用</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>5</td>
<td>70</td>
<td>0.9</td>
<td>0.05</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.05</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

图 门诊心脏监测的成本效益比作为关键变量功能的单因素敏感性分析。基础病例的模型输入变量见表 2.
于卒中的二级预防来说，氯吡格雷或小剂量阿司匹林加用长效双嘧达莫可能会稍优于单用阿司匹林，但最近的研究表明这种差异非常微妙[43]，在我们的模型中可能没有显著性意义。在评估我们的患者人群服用阿司匹林的每年卒中风险时，我们最初参考了两个比较华法林和阿司匹林预防AF患者卒中复发的随机试验[44,45]。但是在这个强化降脂[46]和严格控制血压的时代[47]，上述两项研究中服用阿司匹林的AF患者的卒中年复发率很可能低于9%-10%[44,45]。在最近的一项研究中，那些患有AF并有卒中或短暂性脑缺血发作(TIA)史的、不能使用华法林而服用阿司匹林的患者，每年卒中复发率为6.3%[48]。保守估计，我们推测服用阿司匹林的卒中复发率为4.5%。

需要注意的是，尽管强效降脂和严格血压控制减少了AF患者的总的卒中复发率，华法林预防卒中复发仍优于抗血小板治疗[42]，因此我们关于华法林有效性的假设仍然可行。进一步讲，尽管有更先进的预防AF的方法，如直接凝血酶抑制剂dabigatran[49]和经皮关闭左房心耳的设备[50]，可在临床上这些治疗还没有被广泛证明和采用。目前，华法林仍是AF患者预防血栓栓塞的金标准[51]。

为了检验年龄对门诊心脏监测的成本效用的影响，在模型中我们使年龄在65-90岁中变化。假设在这个年龄范围内卒中的几率是恒定的，我们发现对于年轻患者门诊心脏监测更具成本效用；这可能是因为伴有AF年轻患者有更高的卒中累积风险，以及年轻的卒中患者存活时期长，护理花费高。但是，这项分析没有考虑到年轻患者比年老患者卒中年发病风险低。此外，我们的敏感性分析不包括年龄<65岁的患者，所以我们的结果不能扩展到年轻的卒中患者，在我们的模型中假定的参数对其不合适。

在为我们的基础病例选择花费变量时，我们使用监测一周的费用，因为几乎没有数据是关于长期监测的。但是，门诊心脏事件监测通常在30天内是可报销的[52]。30天的门诊心脏监测花费为284-783美金，平均532美金[23,53]。在我们的敏感性分析中可看出，即使没有假定从更长的监测中能够获取更多收益，门诊监测在这个范围内仍是有效成本效益的。我们的模型假设自然触发的、非意愿性的、表面回路的检测仪为最经济和理想的选项。大量不同的设备和仪器可用来进行门诊流动心电描记；不同的选择包括：植入性电极或表面电极，技术员或内科医师实时阅读记录，患者记录或自动触发记录，自动数据传输或人工数据传输。患者触发事件记录仪不
对患者生活质量的影响。研究发现偶然发现的疾病可能增加焦虑和抑郁症状以及旷工事件[59-60]，门诊监测发现的AF或其他无症状心律失常有相似的不良影响。但是基于这些研究对生活质量的影响却很小。此外，将偶然发现的、不影响患者寿命的无症状疾病对患者生活质量的降低与监测发现的AF带来的致残率下降及生命年的延长直接相对比是不合适的[60]。在任何情况下，在合理范围内改变偶然发现心律失常的患者的剩余生存年数不影响成本效用比。

最后，成本效用分析最好能从社会的角度来进行[90]。严格的说，我们的分析没有做到，因为我们排除了护理者的费用。但是因为监测预期能够减少卒中的复发并减少护理需要，将护理者费用包括进去可能将增加门诊心脏监测的成本效用。

小结

我们的分析提示缺血性卒中后进行一周的门诊心脏监测有成本效用。2006美国心脏病学会和美国卒中学会的指南推荐急性缺血性卒中患者进行心脏监测以发现重要的心律失常，包括AF[90]。指南注意到尚无临床试验提出最佳监测时间，因此报告了一个大致的共识，即监测最少持续24小时。多项研究表明长于24小时的监测能发现更多的AF[6-11]，但也有观点反对门诊心脏监测，因为其缺乏成本效益[55,57]。所以，我们的研究将为指南推荐常规门诊心脏监测提供依据。随着更多门诊心脏监测收益的数据的发表，我们将分析将更有说服力。但即使仅有现在的数据，我们仍建议原因不明的卒中患者进行至少一周的门诊心脏监测以发现潜在的AF。

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