Cost Effectiveness of Warfarin Versus Aspirin in Patients Older Than 75 Years With Atrial Fibrillation

Sue Jowett, PhD; Stirling Bryan, PhD; Jonathan Mant, MD; Kate Fletcher, BA; Andrea Roalfe, MSc; David Fitzmaurice, MD; Gregory Y.H. Lip, MD; F.D. Richard Hobbs, FMedSci

Background and Purpose—Oral anticoagulants are effective at reducing stroke compared with aspirin in atrial fibrillation patients older than 75 years. Although the benefits of reduced stroke risk outweigh the risks of bleeding, the cost effectiveness of warfarin in this patient population has not yet been established.

Methods—An economic evaluation was conducted alongside a randomized, controlled trial; 973 patients ≥75 years of age with atrial fibrillation were recruited from primary care and randomly assigned to either take warfarin or aspirin. Follow-up was for a mean of 2.7 years. Costs of thrombotic and hemorrhagic events, anticoagulation clinic visits, and primary care utilization were determined. Clinical benefits were expressed in terms of a primary event avoided: fatal/nonfatal disabling stroke, intracranial hemorrhage, or systemic embolism. A cost-utility analysis was performed using quality-adjusted life years as the benefit measure.

Results—Total costs over 4 years were lower in the warfarin group (difference, −£165; 95% CI, −£452–£89), primarily driven by the difference in primary event costs. The primary event rate over 4 years was lower in the warfarin group (0.049 versus 0.099), and the quality-adjusted life years score was higher (difference, 0.02; 95% CI, −0.07–0.11). With lower costs and a higher quality-adjusted life years score, warfarin is the dominant treatment, but the differences in both costs and effects are small.

Conclusions—Warfarin is cost-effective compared with aspirin in atrial fibrillation patients age ≥75 years. These data support the anticoagulant therapy option in this high-risk patient population. However, the small differences in costs and effects indicate the importance of exploring patient preferences. (Stroke. 2011;42:1717-1721.)

Key Words: economic evaluation ■ warfarin ■ aspirin ■ atrial fibrillation

Atrial fibrillation (AF) affects 12% of people ≥75 years of age,1 and more than half of all people with AF are in this age group.2 AF is a major cause of morbidity and mortality, as it is a major risk factor for stroke, with a five-fold increase in risk in stroke compared with adults without AF.3

Anticoagulation therapy (warfarin) has been established as a highly effective treatment for reducing stroke risk. The Birmingham Atrial Fibrillation Treatment in the Aged (BAFTA) trial has confirmed that this is the case for AF patients ≥75 years of age, with warfarin shown to be more effective than aspirin and as safe in the prevention of stroke.4-5 However, there is limited evidence regarding the cost effectiveness of warfarin in this age group. Previous economic evaluations have typically relied on effectiveness and safety data from clinical trials where patients ≥75 years of age are underrepresented.6-8 It is conceivable that any cost savings through reduction in stroke incidence may be lost with the additional monitoring costs required by warfarin. This article reports the cost-effectiveness analysis conducted alongside the first randomized, controlled trial of warfarin versus aspirin in a primary care AF population of patients ≥75 years of age.4 The aim of this study was to determine the cost effectiveness of warfarin in this patient population.

Methods

Overview

A trial-based cost effectiveness analysis was conducted alongside the BAFTA trial with mean patient follow-up of 2.7 years. Clinical benefits were expressed in terms of primary and secondary events avoided. The economic evaluation took the form of a cost-utility analysis using quality-adjusted life years (QALYs) as the benefit measure. QALYs take into account the survival and quality of life of an individual; the focus here was on both the potential for quality of life gains from a reduction in clinical events, and on the effect that treatment may have on quality of life. Full details of the trial methods and results have been previously published.4-5 The trial recruited 973 patients ≥75 years of age with AF, and patients were randomized to warfarin (target international normalized ratio, 2.5, with acceptable range 2–3) or aspirin (75 mg daily).

Health Outcomes

The primary outcome of the trial was first occurrence of fatal or nonfatal disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, or systemic embolism. Secondary outcomes were major extracranial hem-
extrapolation of the health utility curve. This was performed using a linear interpolation method, and the results were adjusted for baseline differences using a regression-based adjustment. A quality of life questionnaire was administered to study participants at baseline, and it was repeated annually thereafter. The questionnaire contained the EQ-5D (EuroQol Group), a generic tool that measures and values health-related quality of life. Utility values derived from a UK general population survey were used. The QALY score for each study patient over their duration of follow-up in the trial was estimated by calculating the area under each patient’s health utility curve using linear interpolation. Multiple imputation was used in cases of missing EQ-5D data at 1 or more of the time points. To avoid bias, adjustment for differences in baseline EQ-5D scores was also performed using a regression-based adjustment. All QALYs scores reported in this article reflect imputation and adjustment.

Cost Analysis

The cost analysis adopted a UK health sector perspective, with health resource use data collected on all trial patients. Resource use data concentrated on 3 main areas: clinical events, primary care visits, and warfarin clinic visit costs. Primary and secondary outcome data on clinical events were obtained from primary care records, hospital records, and death certificates. Details of all clinical events were sent to the end point committee (primary outcomes) and to independent consultants for verification. Data on type and frequency of primary care visits were collected from patient records. Data on international normalized ratio tests were collected from the oral anticoagulation service provider. A questionnaire was sent to each participating practice to determine the predominant type of anticoagulation clinic their warfarin patients attended. The type of anticoagulation clinic attended and the total number of clinic visits were recorded for every patient. Unit costs for each model of anticoagulation clinic were obtained from a previous study. For all trial patients, clinical events were recorded and events requiring hospitalization were mapped to UK Healthcare Resource Group codes for nonacute inpatient stays in the National Health Service reference costs; this took into account use and health-related quality of life after the clinical event (ie, the primary end point). Costs incurred by patients after a primary event in addition to the acute secondary care costs included primary care visits, warfarin clinic visits, and long-term care. For primary care and warfarin clinic attendances, resource use rates for each patient in the preceding period in the trial were calculated and applied to the post-event period. Long-term care costs were assumed to apply if a patient had suffered a disabling event, primarily stroke, and literature-based estimates of quality of life were applied in the absence of patient self-report data.

Cost-Effectiveness Analysis

An incremental cost-effectiveness analysis was conducted, based on intention to treat, to determine the difference in costs and outcomes between warfarin and aspirin. Even though the cost data are skewed, the arithmetic mean was calculated, along with its nonparametric 95% CI. To account for uncertainty caused by sampling variation in cost-effectiveness, nonparametric bootstrap- ing was applied to the patient level data to derive 5000 paired estimates of mean differences in costs and QALYs scores. These were presented graphically on a cost-effectiveness plane.

Three sets of sensitivity analyses were performed. First, the effect of nonadjustment of QALYs for the difference in baseline EQ-5D values was explored. Second, costs and QALYs for shorter follow-up periods were calculated to investigate whether costs and outcomes changed with length of follow-up. Finally, analyses were performed for 3 subgroups of age.

STATA for Windows, Version 15.0 was used to perform part of the main statistical analysis. Bootstrapping was carried out using STATA Version 8.2, and Microsoft Excel 2002 SP3 was used to construct the cost-effectiveness acceptability curves. Multiple imputations were performed using NORM Version 2.03.

Results

A total of 973 patients were entered into the study (warfarin, 488, versus aspirin, 485). Trial participants had a mean age of 81.5 years (SD, 4.2), and 55% were men. The baseline characteristics in terms of key variables were similar in both arms of the trial. The baseline EQ-5D score was higher in the warfarin arm (0.757; SD, 0.241) than in the aspirin arm (0.735; SD, 0.215). Two warfarin patients were excluded from the cost-effectiveness analysis, as they withdrew very early in the trial and so no data on costs or quality of life were collected. Complete EQ-5D data were available for 462 patients (47.6%), with a higher completion rate in the aspirin arm (50.3%) compared with the warfarin arm (44.7%). The majority of patients with missing data were missing fewer than 2 EQ-5D scores.

Health Outcomes and Quality of Life

There were fewer primary events in the warfarin arm than in the aspirin arm (24; 1.8%/year, versus 48; 3.8%/year). The primary event rate for the 4-year period was also calculated for each trial arm (Table 1) and showed a significant difference in event rates.
The results of our analysis show that warfarin may be a cost-effective therapy for patients with AF ≥75 years of age; this is primarily because of the difference in primary event rates, as this drives the difference in costs. The additional costs for international normalized ratio tests for warfarin were offset by the primary event costs. A previous Swedish analysis demonstrated that the cost-effectiveness of warfarin is very much dependent on the rate of hemorrhagic complications, which was no higher than in those with aspirin in this trial.

Other model-based studies assessing the cost-effectiveness of warfarin in AF patients have shown warfarin to be cost-effective, particularly in groups of patients with a higher baseline risk of stroke; this includes those in this older age group. However, data on the effectiveness of warfarin and aspirin in more elderly patients have been from trials where the majority of patients were younger than 75 years; hence there is a particular need for age-specific data. It is reassuring that the results of this trial-based analysis are consistent with those of these previous model-based analyses.

Quality of life and cost differences were small between the 2 trial arms and may be caused by the analysis being underpowered for these variables. Potential adverse effects of warfarin on quality of life (eg, regular clinic visits and associated side effects, including minor bleeds) may not have been translated into detectable differences in the EQ-5D questionnaire. Previous studies have demonstrated that AF patients attribute some disutility to being on warfarin (compared with full health). One of the disadvantages of warfarin is regular clinic visits, which can be inconvenient if the patient is employed; however, this was not an issue for the BAFTA study population. Even so, as the cost and QALYs differences are quite small, and there are competing benefits and disadvantages of warfarin and aspirin, patient preferences for treatment need to be considered.

A key strength of this work is that the trial was conducted in primary care and used data from a large, contemporary, randomized, controlled trial, designed specifically to address the question of warfarin use in an older population. As data was collected at a patient level, the analysis could consider uncertainty around the mean costs and outcomes. There are some limitations. Over half of patients did not have complete EQ-5D data for the full duration of their follow-up; however, the variability around mean values is higher.

## Cost-Effectiveness Analysis

Tables 2 and 3 give a breakdown of resource use data and mean health care costs per patient over a 4-year period. The intention-to-treat principle was maintained throughout the analysis. Event costs were higher in the aspirin arm, primarily driven by the difference in primary events. Primary care visit costs were slightly higher in the warfarin arm, and international normalized ratio visit costs were considerably greater as expected. Total costs per patient were higher in the aspirin group than in the warfarin group (£1548 versus £1382), but the difference was not statistically significant.

The warfarin arm was associated with lower costs and a higher QALYs score than was the aspirin arm, indicating that warfarin is the dominant treatment option. However, to take into account uncertainty around the point estimates, an incremental cost-effectiveness plane and cost-effectiveness acceptability curve were constructed. The plane in Figure 1 shows the 5000 bootstrap cost-QALYs difference pairs, most of which are in the southwest and southeast quadrants; this indicates that warfarin is less costly, with a greater proportion in the southeast quadrant where the treatment is more effective (ie, positive incremental QALYs scores).

### Sensitivity Analysis

Tables 4 and 5 present the results of the sensitivity analysis. If the baseline difference in quality of life is ignored, the difference in QALYs scores between warfarin and aspirin is greater. Here there is a difference of 0.06 QALYs (favoring warfarin) compared with the base-case analysis, where the difference in adjusted scores is 0.02; this demonstrates the impact of the baseline difference. Calculating total cost and QALYs over a shorter period serves only to reduce the differences in costs and QALYs, but the overall finding of dominance for warfarin remains. Considering the results by age group, similar results of small cost and QALYs differences are found across all age groups, with the cost and QALYs difference greatest for those age 75 to 79 years. However, compared with the base-case analysis, the subgroups obviously include fewer patients, and so the variability around mean values is higher.

### Discussion

The results of our analysis show that warfarin may be a cost-effective therapy for patients with AF ≥75 years of age;

### Table 2. Mean Resource Used by Treatment Arm

<table>
<thead>
<tr>
<th>Event or Visit</th>
<th>Warfarin (n=486)</th>
<th>Aspirin (n=485)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary event</td>
<td>0.049</td>
<td>0.099</td>
</tr>
<tr>
<td>Secondary vascular event</td>
<td>0.206</td>
<td>0.191</td>
</tr>
<tr>
<td>Major haemorrhagic event</td>
<td>0.037</td>
<td>0.041</td>
</tr>
<tr>
<td>Primary care visit</td>
<td>28.34</td>
<td>27.53</td>
</tr>
<tr>
<td>INR visit</td>
<td>17.53</td>
<td>3.47</td>
</tr>
</tbody>
</table>

INR indicates International Normalized Ratio (warfarin clinic visit).

*Accrued by 82 patients who were switched from aspirin to warfarin during the course of the trial.

### Table 3. Mean Total Costs per Patient Over 4 Years

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n=486)</th>
<th>Aspirin (n=485)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost (£)</td>
<td>Mean SD</td>
<td>Mean SD</td>
</tr>
<tr>
<td>All events</td>
<td>542 1117</td>
<td>724 1380</td>
</tr>
<tr>
<td>Primary events</td>
<td>173 622</td>
<td>318 810</td>
</tr>
<tr>
<td>Secondary vascular events</td>
<td>317 905</td>
<td>328 969</td>
</tr>
<tr>
<td>Haemorrhagic events</td>
<td>52 340</td>
<td>78 488</td>
</tr>
<tr>
<td>Primary care visits</td>
<td>507 435</td>
<td>483 369</td>
</tr>
<tr>
<td>INR visits</td>
<td>191 217</td>
<td>38 106</td>
</tr>
<tr>
<td>Long-term cost</td>
<td>143 1215</td>
<td>304 1575</td>
</tr>
<tr>
<td>Total cost</td>
<td>1382 2004</td>
<td>1548 2468</td>
</tr>
</tbody>
</table>

Difference in total cost (95% CI) (-166 to 166)

INR indicates International Normalized Ratio (warfarin clinic visit).
in many cases, this was trial protocol-driven because of the absence of quality of life data collection beyond a primary endpoint. We found no evidence of a major difference in the 2 drugs in terms of effect on quality of life, so the imputation is unlikely to have had a major impact on the results; these results were primarily driven by the differences in primary event rate, for which data were complete for the trial period.

Conducting an economic evaluation alongside an endpoint trial poses problems. In this study, data collection ceased once a primary endpoint occurred, so there was no additional information on quality of life of the patients, or on subsequent health service use. To address this, we have extrapolated both costs and quality of life for up to 4 years post-recruitment, using previously published data from the literature.17,18 We assumed that all patients who have suffered a particular major clinical event will be in the same health state and incur the same long-term costs. Another consideration is the transferability of the results to usual (non-trial) care, both in the UK and internationally. Doctors whose patients were recruited into the trial may have different prescribing preferences with those who did not participate. Furthermore, the results of the economic evaluation are for the UK health care system and the UK model of anticoagulation clinics, and so caution is required in seeking to transfer our results to other health care systems.

In the present study, National Health Service reference costs were used to obtain the costs of an “average event” for the clinical events suffered by trial patients. However, because the patients in the trial were older than was the patient population from whom the average cost was obtained, it is likely that the events were more costly in this patient group. Thus, we are likely to have underestimated the cost-effectiveness of warfarin.

Long-term costs and benefits, such as acute or ongoing costs related to future events and effects on quality of life or survival, were not taken into account beyond a 4-year period. If we had employed a lifetime horizon, it is likely that the advantages of warfarin over aspirin would have been greater; our sensitivity analysis showed that an increasing time horizon resulted in a bigger difference in benefits and costs between warfarin and aspirin.

In conclusion, our analyses show that warfarin appears to be a cost-effective use of health care resources for the management of patients with AF ≥75 years of age. While
warfarin should be considered routinely as an option in the management of such patients, it is particularly important in this context that patients’ preferences are considered when a decision about treatment is made.

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**Disclosures**

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**References**


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**Table S1 Unit costs**

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<th>Event Type</th>
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<td>Ischaemic or unknown stroke, disabling or fatal</td>
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<td></td>
<td>Haemorrhagic stroke/intracerebral haemorrhage (fatal and non-fatal)</td>
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<td></td>
<td>Systemic embolism (fatal and non-fatal)</td>
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<td>Transient Ischaemic Attack</td>
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<td><strong>Primary events: long-term costs (per day)</strong></td>
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<td>Systemic embolism</td>
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<td><strong>Secondary vascular events: acute costs</strong></td>
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<td>Pulmonary Embolus</td>
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<td>Heart failure</td>
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<td>Angina</td>
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<td><strong>Anticoagulation clinics</strong></td>
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<td></td>
<td>Practice NPT clinic</td>
<td>15.99</td>
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DA. Patient self-management of anticoagulation therapy: a trial-based cost-
Abstract 14

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(Stroke. 2011;42:1717-1721.)

Key Words: economic evaluation ■ warfarin ■ aspirin ■ atrial fibrillation

배경과 목적
심방세동(attrial fibrillation)이 있는 75세 이상의 환자에서 경구 항응고제(oral anticoagulant)는 아스피린에 비해 뇌출 증을 줄이는 데 효과적이다. 비록 뇌출증 위험 감소 효과가 출혈 위험을 늘리나, 이러한 환자군에서 와파린의 비용효과는 아직 연구된 바 없다.

방법
경제성 평가는 나란한( alongside) 무작위 배정 대조 연구로 시행하였다: 심방세동이 있는 75세 이상의 환자 973명이 임차 진료를 통해 모집되었으며, 와파린이나 아스피린을 복용하도록 무작위 배정되었다. 평균 2.7년 동안 추적 관찰하였다. 혈전성 또는 출혈성 사고, 항응고 클러니 행황, 임차 진료 이용의 비용을 고려하였다. 임상적 유용성은 치명적/비치명적인 장애가 있는 뇌출증, 두개내출혈(intracranial hemorrhage), 또는 전신의 색전증(systemic embolism)과 같은 주요 사건이 없는 경우로 설정되었다. 비용 효용 분석(cost–utility analysis)은 질보정 생존년수(quality–adjusted life years, QALY)를 이용 측정 기준으로 사용하였다.

결과
4년이 넘는 기간 동안 종 비용은 와파린군에서 더 높았고(차이, -£165; 95% CI, -£452~£89), 이는 주로 주요 사건 발생의 비용 차이로 인한 결과였다. 4년이 넘는 기간 동안 주요 사건 발생률은 와파린군에서 더 낮았으며(0.049 vs. 0.099), QALY 점수는 더 높았다(차이, 0.02; 95% CI, -0.07~0.11). 낮은 비용과 높은 QALY 점수를 보면 와파린이 더 좋은 치료이나, 비용과 효과 모두 그 차이는 작았다.

결론
와파린은 심방세동이 있는 75세 이상의 환자에서 아스피린에 비해 비용효과적이다. 이러한 자료는 고위험 환자군에서 항응고제 치료 선택을 뒷받침한다. 그러나 비용과 효과는 그 차이가 작으므로, 환자의 선호도를 고려하는 것이 중요한 것이다.