Warfarin Versus Aspirin for Prevention of Cognitive Decline in Atrial Fibrillation
Randomized Controlled Trial (Birmingham Atrial Fibrillation Treatment of the Aged Study)

Nahal Mavaddat, PhD; Andrea Roalfe, MSc; Kate Fletcher, PhD; Gregory Y.H. Lip, MD; F.D. Richard Hobbs, FMedSci; David Fitzmaurice, MD; Jonathan Mant, MD

Background and Purpose—Atrial fibrillation is associated with decline of cognitive function. Observational evidence suggests that anticoagulation might protect against this decline. We report the first randomized controlled trial evidence on the effect of anticoagulation on cognitive function in elderly patients with atrial fibrillation.

Methods—A total of 973 patients aged ≥75 years with atrial fibrillation were recruited from primary care and randomly assigned to warfarin (n=488; target international normalized ratio, 2–3) or aspirin (n=485; 75 mg/d). Neither participants nor investigators were masked to group assignment. Follow-up was for a mean of 2.7 years (SD, 1.2). Cognitive outcome was assessed using the Mini-Mental State Examination at 9-, 21-, and 33-month follow-up. Participants who had a stroke were censored from the analysis, which was by intention to treat with imputation for missing data.

Results—There was no difference between mean Mini-Mental State Examination scores in people assigned to warfarin or aspirin at 9 or 21 months. At 33-month follow-up, there was a nonsignificant difference of 0.56 in favor of warfarin that decreased to 0.49 (95% confidence interval, –0.01 to 0.98) after imputation.

Conclusions—We found no evidence that anticoagulation confers clinically important protection over aspirin against cognitive decline as measured by the Mini-Mental State Examination in atrial fibrillation in the first 33 months of treatment other than that provided by preventing clinical stroke.


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Key Words: aspirin ■ atrial fibrillation ■ cognition ■ warfarin

Stroke is associated with significant cognitive decline and dementia.1,2 Cognitive deficit may also occur in people with atrial fibrillation (AF) in the absence of stroke.3 An association between the presence of atrial fibrillation and cognitive deficit as measured by, for example, the Mini-Mental State Examination (MMSE), has been reported in a number of cross-sectional studies in hospital and community settings after controlling for a range of covariates, such as previous transient ischemic attack or stroke, cardiovascular risk factors, other cardiovascular disease, medications, and depression.3–9 A systematic review of 15 prospective studies found that AF was associated with an increased risk of cognitive decline in people with stroke, but the association was only of borderline significance in people without stroke.2 A subsequent post hoc analysis of 2 randomized controlled trials involving 31506 participants found that AF was associated with an increased risk of cognitive decline and dementia in both people with and without stroke.3

Cognitive function was a secondary outcome in the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), whose main findings were reported in 2007.9,10 It is known that anticoagulation reduces the risk of stroke in AF,11 and that stroke leads to impaired cognitive function.1 Therefore, it can be inferred that anticoagulation reduces risk of cognitive decline in AF by preventing overt strokes. What is not known is whether anticoagulation reduces the risk of cognitive decline in AF through any other mechanism, such as by reducing the risk of silent stroke. The aim of this analysis is to compare the efficacy of warfarin with aspirin for prevention of cognitive decline in a primary care population of
people aged ≥75 years who have AF, excluding effects on risk of clinical stroke.

Methods
Study Design and Participants
BAFTA was a pragmatic prospective randomized open-label trial with unblinded assessment of cognitive function. Patients with AF were recruited from 260 general practices in England and Wales between April 2001 and November 2004. Inclusion criteria were aged ≥75 years with AF demonstrated by a study ECG or by an ECG done within the previous 2 years. Patients were excluded if they had rheumatic heart disease; major nontraumatic hemorrhage within the previous 5 years; intracranial hemorrhage; endoscopically proven peptic ulcer disease in the previous year; oesophageal varies; terminal illness; surgery within the previous 3 months, blood pressure >180/110 mm Hg, or if their primary physician judged that they should or should not be on warfarin. The majority of the patients (87%) were free of stroke at baseline. Before randomization, patients were assessed for cognitive function using the short orientation-memory concentration test. This has been shown to correlate closely with the MMSE and, given its brevity, was used in preference to the MMSE for baseline screening to minimize respondent burden. Those with a score of ≥210 were excluded unless they had a carer who was responsible for their medication.

Randomization was stratified into 6 groups on the basis of sex and age (75–79, 80–84, and ≥85 years) in blocks of 8. Allocations were made by the Birmingham Cancer Trials Unit when telephoned by a primary care physician. The study was approved by the West Midlands Multi-center Research Ethics Committee (MREC/99/7/57). Written informed consent was obtained from all participants.

Procedures
Patients assigned aspirin were prescribed 75 mg daily. Those assigned warfarin were treated with a target international normalized ratio (INR) of 2.5, with an acceptable range of 2 to 3. Frequency of INR testing ranged from weekly or less if control needed to be achieved, to ≤12 weeks if the INR was stable. Neither participants nor investigators were masked to group assignment.

The primary outcome for the main study was first occurrence of fatal or nonfatal disabling stroke (ischemic or hemorrhagic), other intracranial hemorrhage, or clinically significant arterial embolism. Cognition was assessed using the MMSE, administered by a primary care clinician at 9-, 21-, and 33-month face-to-face follow-up. Formal training on how to administer the MMSE was given to practitioners before participation in the trial. The MMSE is a score of cognitive impairment addressing 6 components of function: orientation (time and place), registration, attention, recall, language, and praxis and has been validated in a number of populations. Scoring is out of 30, with scores increasing in relation to correct responses. Data on INR control were obtained from primary care and hospital records.

If a patient experienced a primary end point, then follow-up ceased. For this analysis, patients were also censored if they experienced a nondisabling stroke. This was done to exclude the direct effect of prevention of clinical stroke on the results because it has already been established that warfarin reduces stroke risk relative to aspirin. Follow-up ceased in September 2006 at the planned termination of the research funding. As a result, some patients were not in the study for sufficient time to have a 33-month follow-up.

Statistical Analysis
A sample size of 52 in each treatment arm was required to detect a clinically important 2 U difference in MMSE assuming SD=3.1 at the 5% significance level with 90% power.

Repeated measures mixed modeling was used to compare MMSE scores between groups at each of the follow-up at 9, 21 and 33 months. Short orientation-memory concentration test completed at baseline was included as a covariate. Additional analysis also adjusted for age, sex, and history of stroke or transient ischemic attack. The MMSE scores were negatively skewed; therefore, bootstrapped estimates (1000 replications) were obtained to improve the accuracy of the results.

Under the assumption that unobserved values were missing at random, missing data were imputed at the relevant time points at which participants were eligible for follow-up. Data were not imputed after a patient died, if follow-up ceased before the 33-month time point had been reached. Multiple imputation was undertaken using the imputation by chained equations procedure in Stata (12). Variables included in the imputation were age, sex, history of stroke/transient ischemic attack, baseline short orientation-memory concentration test, randomization group, and MMSE. Following Rubin recommendations, 10 imputations were performed, and bootstrapped repeated measures mixed modeling was performed on each imputed data set. The adjusted mean and confidence intervals from each analyses were then consolidated using Rubin rules.

Figure 1. Trial profile. MMSE indicates Mini Mental State Examination.
Table 1. Distribution of Short Orientation-Memory Concentration Test at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>488</td>
<td>485</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2 (0–4)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.8 (3.4)</td>
<td>2.9 (3.4)</td>
</tr>
<tr>
<td>Normal (0–7)</td>
<td>439 (90.0%)</td>
<td>439 (90.5%)</td>
</tr>
<tr>
<td>Mild impairment</td>
<td>31 (6.4%)</td>
<td>25 (5.2%)</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>15 (3.1%)</td>
<td>16 (3.3%)</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>2 (0.4%)</td>
<td>4 (0.8%)</td>
</tr>
</tbody>
</table>

Two short orientation-memory concentration test results were missing, 1 in each group. IQR indicates interquartile range.

To check whether the missing at random assumption was appropriate, we plotted MMSE scores according to follow-up status: follow-up complete; follow-up complete until occurrence of death, stroke, or other primary end point; follow-up complete, but patient in study for <33 months; follow-up incomplete.

We conducted sensitivity analyses using different approaches to multiple imputation of the 33-month data: (1) last value carried forward; (2) imputed value reduced by 2 U; (3) imputed value reduced by 3 U. The latter analyses were performed because cognitive impairment is as an independent risk factor for attrition in longitudinal studies in older people.

MMSE was categorized into 4 groups (scored [0–30] according to National Institute for Health and Care Excellence classification: 0–9 severe impairment, 10–20 moderate impairment, 21–24 mild impairment, 25–30 normal). Generalized mixed modeling was used to examine the association between cognition classification and drug treatment over time (proportional odds assumption being confirmed).

The odds represent likelihood of better cognition if treated with warfarin rather than aspirin across the range of cognition groups. All analyses were by intention to treat.

Results

A total of 973 participants entered the study (Figure 1). Mean age of participants was 81.5 years (SD, 4.3; range, 75–94) and 54.6% were men. Previously reported baseline characteristics were similar in terms of age, sex, risk factors for stroke, history of stroke/transient ischemic attack, heart failure (20% of study population), diabetes mellitus (14% of study population), and hypertension (54%) in people randomized to warfarin and to aspirin.

INR control on warfarin was within therapeutic range 67% of the time. A total of 3.8% of participants had moderate or severe cognitive impairment (Table 1). A total of 80% of eligible participants (78% in warfarin arm and 83% in aspirin arm) had complete MMSE data at 9 months, 69% (67% warfarin arm and 72% aspirin arm) at 21 months, and 57% (55% warfarin arm and 59% aspirin arm) at 33 months (Figure 1). A total of 163 participants were not followed up by 33 months because they had died (81 in the warfarin arm and 82 in the aspirin arm), and 50 (16 in the warfarin arm and 34 in the aspirin arm) because they had a nonfatal primary end point or non-disabling stroke. A further 339 participants were not followed up at 33 months because the study was terminated before this time point was reached.

Frequency of MMSE scores at each follow-up point by treatment allocation is shown in Figure 1 in the online-only Data Supplement. Table 2 shows the proportions of people with different degrees of cognitive impairment at different time points—there were no significant differences. After 9-month follow-up, there was no difference in mean MMSE between treatment groups (Figure 2; Table 3). By 33 months, there were nonsignificant differences in favor of warfarin of 0.56 on adjusted analysis and 0.49 after multiple imputation. An apparent widening of the difference in cognitive function between groups over time was not statistically significant (Table 3).

MMSE scores of people with incomplete follow-up were similar to those of people with complete follow-up (Figure 3).

Using different assumptions for multiple imputation had minimal effect on the results at 33 months. Using last value carried forward, reducing the value by 2 U and by 3 U led to a difference in mean scores of 0.27 (95% confidence interval, –0.22 to 0.76; P=0.23), 0.40 (95% confidence interval, –0.10 to 0.90; P=0.19), and 0.36 (95% confidence interval, –0.15 to 0.87; P=0.26), respectively.

Discussion

We found no evidence that anticoagulation confers clinically important protection against cognitive decline in AF in the first 33 months of treatment in addition to that provided by preventing clinical stroke. We did find higher cognitive

Table 2. Distribution of Cognitive Function Class at 9-, 21-, and 33-Month Follow-Up by Treatment Allocation

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Group</th>
<th>Normal (25–30)</th>
<th>Mild Impairment (21–24)</th>
<th>Moderate Impairment (10–20)</th>
<th>Severe Impairment (0–9)</th>
<th>Odds Ratio* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mo</td>
<td>Warfarin</td>
<td>299 (84%)</td>
<td>41 (12%)</td>
<td>14 (4%)</td>
<td>1 (0.3%)</td>
<td>Unadjusted</td>
<td>1.03 (0.41–2.58)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>308 (81%)</td>
<td>53 (14%)</td>
<td>17 (5%)</td>
<td>0 (0%)</td>
<td>Adjusted†</td>
<td>1.24 (0.67–2.31)</td>
</tr>
<tr>
<td>21 mo</td>
<td>Warfarin</td>
<td>244 (87%)</td>
<td>28 (10%)</td>
<td>10 (4%)</td>
<td>0 (0%)</td>
<td>Unadjusted</td>
<td>1.82 (0.66–5.03)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>243 (84%)</td>
<td>36 (12%)</td>
<td>11 (4%)</td>
<td>1 (0.3%)</td>
<td>Adjusted†</td>
<td>1.60 (0.78–3.26)</td>
</tr>
<tr>
<td>33 mo</td>
<td>Warfarin</td>
<td>101 (84%)</td>
<td>15 (13%)</td>
<td>4 (3%)</td>
<td>0 (0%)</td>
<td>Unadjusted</td>
<td>1.43 (0.40–5.10)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>92 (78%)</td>
<td>19 (16%)</td>
<td>7 (6%)</td>
<td>0 (0%)</td>
<td>Adjusted†</td>
<td>1.48 (0.56–3.91)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
*Odds ratio >1 indicates higher odds of improved cognition with warfarin.
†Adjusted by baseline short orientation-memory concentration test, age, sex, and previous stroke or transient ischemic attack.
function as measured by the MMSE in people aged ≥75 with AF assigned to warfarin when compared with those assigned to aspirin after 33 months of follow-up, but this difference was not statistically significant in either the complete case or multiple imputation analyses, making allowance for missing cognition data (43% of study participants at 33 months). There were no differences in the proportion of people with severe, moderate, or mild impairment by treatment group at any time point and the observed difference between arms of 0.49 (−0.01 to 0.98) is less than what is regarded as clinically significant (2–4 U on the MMSE).15,18,19 Given that the upper limit of the confidence interval is <2, we have excluded the possibility of a clinically important effect on cognitive function of warfarin in AF within 33 months of treatment onset.

This result needs to be interpreted in the light of several features of the study. First, follow-up ceased if a patient had a stroke, so the effects we observed are separate from the effect of anticoagulation on stroke prevention. This distinguishes this trial from other cardiovascular risk management trials of people at high risk of stroke, such as the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, where follow-up of MMSE included people who had strokes during the trial.20 Our decision to censor patients who had a stroke meant that we were unable to explore any potential interaction between stroke and cognitive outcome. Second, the control arm was an active drug (aspirin) rather than a placebo. A systematic review of observational studies (not in AF) found that long-term use of nonsteroidal anti-inflammatory drugs was associated with a significant reduction in risk of Alzheimer disease, but evidence from randomized controlled trials is lacking, apart from 1 trial, which found warfarin and aspirin to have similar effects.21,22 Third, although the follow-up period (mean, 2.7 years) was relatively long for anticoagulation in an AF trial, it may not have been long enough to detect differential effect of therapy on cognitive function. Indeed, there is a suggestion in the BAFTA results that differences were widening over time, and this would be consistent with observational evidence on association of other antithrombotic agents (ie, nonsteroidal anti-inflammatory drugs) that the association is stronger with longer follow-up.23 However, a population-based study of cognitive decline found that 59% of the sample showed a cognitive decline of ≥4 U in the MMSE for a 2-year period in people aged ≥81 years, suggesting that 21 to 33 months might be sufficient time for differences to emerge.24 Next, the MMSE has limitations as a measure of cognition especially with regard to executive function and may not have picked up more subtle cognitive differences.24 Nevertheless, it is commonly used as a primary measure of cognitive function in large-scale vascular trials.3,11 Although losses to follow-up were similar in the warfarin and aspirin arms, they were substantial with regard to cognitive outcome measures by 33 months (>40%). However, cognitive function at first follow-up was similar in those who were and were not subsequently followed up (Figure 3), suggesting that this was not a major source of bias. Furthermore, different assumptions for multiple imputation, including a 3-point reduction in MMSE of anyone lost to follow-up, did not result in any important difference in results at 33 months. Therefore, it is unlikely that losses to follow-up masked a clinically important difference in effect of the 2 drugs. Comparison with normative data suggests that our population were more cognitively able than people of similar ages drawn from the general population.25 Nevertheless, our study population, drawn from primary care as opposed to hospital, is likely to be representative of the population for whom anticoagulation would be considered. The study was unblinded, so practitioner recording of MMSE might have been influenced by treatment allocation. It was not feasible to have brain imaging performed on participants as part of the trial procedures, so we were unable to explore the effect of treatments on imaging biomarkers. We used a low dose of aspirin, as is consistent with the evidence

Table 3. Mean Mini-Mental State Examination Score by Treatment Allocation

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted*</td>
<td>26.7</td>
<td>26.7</td>
<td>0.04 (−0.30 to 0.39)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>26.8</td>
<td>26.8</td>
<td>0.01 (−0.33 to 0.34)</td>
</tr>
<tr>
<td>Adjusted and imputed‡‡</td>
<td>26.7</td>
<td>26.7</td>
<td>−0.002 (−0.40 to 0.40)</td>
</tr>
<tr>
<td>21 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted*</td>
<td>27.0</td>
<td>26.8</td>
<td>0.19 (−0.20 to 0.58)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>27.0</td>
<td>26.8</td>
<td>0.15 (−0.22 to 0.53)</td>
</tr>
<tr>
<td>Adjusted and imputed‡‡</td>
<td>26.9</td>
<td>26.7</td>
<td>0.13 (−0.27 to 0.54)</td>
</tr>
<tr>
<td>33 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted*</td>
<td>27.0</td>
<td>26.4</td>
<td>0.62 (−0.01 to 1.24)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>26.9</td>
<td>26.4</td>
<td>0.56 (−0.04 to 1.16)</td>
</tr>
<tr>
<td>Adjusted and imputed‡‡</td>
<td>26.9</td>
<td>26.4</td>
<td>0.49 (−0.01 to 0.98)</td>
</tr>
</tbody>
</table>

Test for trend, P value

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Unadjusted*</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Adjusted†</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Adjusted and imputed‡‡</td>
<td></td>
<td>0.14</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
*Bootstrapped.
†Adjusted by baseline short orientation-memory concentration, age, sex, and previous stroke or transient ischemic attack.
‡Consolidated results from 10 multiply imputed data sets.
base and international guidelines. By the end of the study, a third of patients randomized to warfarin had stopped taking it, and 82 patients who were randomized to aspirin switched to warfarin.

Set against these limitations, a major strength of this analysis is that BAFTA is the only randomized trial of anticoagulation in AF to have reported cognitive function outcomes. The only other evidence from a randomized controlled trial on anticoagulants and cognitive decline was not in an AF population. Given the strong evidence for anticoagulation for stroke prevention in AF that now exists, it is unlikely that there will be any more randomized data on the effect of anticoagulation on cognitive function in AF.

There have been a few observational studies since BAFTA, seeking to identify the effect of anticoagulation in AF on cognitive outcomes, but the results are inconsistent, with one finding benefit of warfarin compared to aspirin, and two finding no difference.

Conclusions
We did not find any important advantage of warfarin instead of aspirin in preventing cognitive decline as measured by the MMSE, but benefit over a longer time period than 33 months cannot be excluded. This analysis could not explore whether anticoagulation might reduce the effect of strokes that do occur on cognitive function. The principal indication for anticoagulation of older people in AF remains stroke prevention.

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Disclosures
None.

References
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