Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

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Summary

Background **Anticoagulants are more effective than antiplatelet agents at reducing stroke risk in patients with atrial fibrillation, but whether this benefit outweighs the increased risk of bleeding in elderly patients is unknown. We assessed whether warfarin reduced risk of major stroke, arterial embolism, or other intracranial haemorrhage compared with aspirin in elderly patients.**

Methods **973 patients aged 75 years or over (mean age 81·5 years, SD 4·2) with atrial fibrillation were recruited from primary care and randomly assigned to warfarin (target international normalised ratio 2–3) or aspirin (75 mg per day). Follow-up was for a mean of 2·7 years (SD 1·2). The primary endpoint was fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN89345269.**

Findings **There were 24 primary events (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in people assigned to warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin (yearly risk 1·8% *vs* 3·8%, relative risk 0·48, 95% CI 0·28–0·80, p=0·003; absolute yearly risk reduction 2%, 95% CI 0·7–3·2). Yearly risk of extracranial haemorrhage was 1·4% (warfarin) versus 1·6% (aspirin) (relative risk 0·87, 0·43–1·73; absolute risk reduction 0·2%, –0·7 to 1·2).**

Interpretation **These data support the use of anticoagulation therapy for people aged over 75 who have atrial fibrillation, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience.**

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Introduction

12% of people aged over 75 years have atrial fibrillation,[1] and 56% of people with this arrhythmia are over the age of 75.[2] Atrial fibrillation is a major risk factor for stroke, leading to a fivefold increase in risk.[3] Because risk of stroke increases with age,[4] stroke prevention in elderly people with atrial fibrillation is a key aspect of management for this group.

Anticoagulation therapy with warfarin is highly effective at reducing stroke risk, but is associated with monitoring costs and a higher risk of haemorrhage compared with other treatments.[5,6] Antiplatelet agents such as aspirin provide a more convenient but less effective alternative.[7] A meta-analysis of individual-patient data from trials showed that anticoagulants are significantly more effective than aspirin at preventing stroke, but that this benefit is at the cost of higher risk of major bleeding.[8] Concerns have been expressed over the applicability of the aforementioned evidence to elderly patients with atrial fibrillation, particularly in primary care settings.[9–12] Older patients were significantly under-represented in the trials: the mean age of participants in trials that compared anticoagulation therapy with no treatment was 69 years,[5] and the mean age of participants in trials that compared anticoagulants with antiplatelet agents was 72 years.[8] In the large Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W),[13] in which treatment with clopidogrel plus aspirin was compared with oral anticoagulation therapy, the mean age of participants was 70 years. This younger age of participants in trials as compared with routine clinical practice is a potential drawback because several studies have shown that risk of serious haemorrhage in patients on anticoagulation increases with age.[14–17] For example, in the Stroke Prevention in Atrial Fibrillation (SPAF) II trial,[18] the annual risk of stroke with haemorrhagic or ischaemic residual deficit was slightly higher in the subgroup of patients aged over 75 years assigned to warfarin as opposed to aspirin (4·6% *vs* 4·3%). In a meta-analysis of data from individual patients aged 75 years or over who were included in trials of aspirin versus anticoagulants, a 2·2% lower risk of ischaemic stroke in those on warfarin was potentially offset by a 1·7% greater risk of a major bleed.[8] However, the CIs around risk of stroke and risk of bleed were wide, because few patients aged 75 years or over were included within the trials. In addition, the frequency of anticoagulant-associated intracerebral haemorrhage has risen substantially through the 1990s, particularly in the elderly, raising further concerns about the possible overuse of anticoagulation.[19]

Evidence from trials of warfarin versus aspirin in primary care populations, which might be at lower risk of stroke than hospital-based populations, is mixed. Although the Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK) study[20] reported lower risk of thromboembolism in patients on warfarin than in those on aspirin, Hellemons and colleagues[21] and Gullov and colleagues[22] in their trials did not show a difference between effects of the treatments; however, these studies[21,22] were underpowered.[23]

Uncertainty over the optimum treatment of elderly people with atrial fibrillation is evident in current guidelines. Guidelines produced jointly by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology for the management of atrial fibrillation[24] recommend use of anticoagulants for patients who have two or more risk factors for stroke (of which age 75 years or over is one), but these guidelines also suggest that patients aged 75 years or older at high risk of bleeding can be treated with a lower international normalised ratio (INR) target than was used in the aforementioned trials.[5,8] Guidelines in England and Wales on the one hand recommend that patients aged 75 years or over with an additional risk factor should be given anticoagulants, but on the other hand recommend that the ages of these patients as a risk factor for haemorrhage should be taken into account.[25] This confusion in guidelines reflects practice, and currently less than half of elderly patients receive warfarin.[26–28]

In view of these uncertainties and concerns over thromboprophylaxis for elderly people who have atrial fibrillation, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study compared the efficacy of warfarin with that of aspirin for the prevention of stroke in a primary care population of patients aged 75 years or over who have atrial fibrillation.

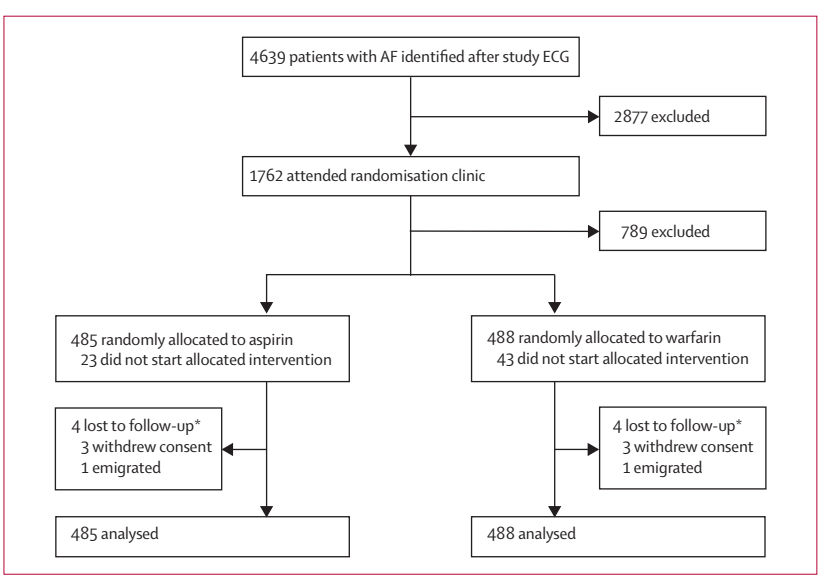

Figure 1: **Trial profile**
AF=atrial fibrillation.

Methods

Study design and participants

BAFTA was a prospective randomised open-label trial with blind assessment of endpoints. The primary aim was to compare the frequency of fatal and non-fatal disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, and other clinically significant arterial embolism in patients who had been randomly assigned to warfarin versus aspirin. The methods used for the BAFTA study are reported in detail elsewhere.[29] Secondary aims were to compare the frequency of major haemorrhage, other vascular events, and all-cause mortality in patients assigned to warfarin versus aspirin. Patients were recruited from 260 general practices in England and Wales between April, 2001, and November, 2004. Patients were eligible for inclusion in the study if they were aged 75 years or over and had atrial fibrillation or atrial flutter demonstrated by a study electrocardiogram (ECG) or by an ECG done within the previous two years. Potential patients were identified through computer searches of primary care records for diagnoses of atrial fibrillation and through opportunistic pulse measurements; patients identified in either way were invited to attend the practice for an ECG, and evidence of atrial fibrillation was verified by a consultant cardiologist. Patients were excluded if they had any of the following: rheumatic heart disease; a major non-traumatic haemorrhage within the previous 5 years; intracranial haemorrhage; endoscopically proven peptic ulcer disease in the previous year; oesophageal varices; allergic hypersensitivity to either of the study drugs; a terminal illness, as judged by their primary care physician; surgery within the past 3 months; or blood pressure greater than 180/110 mm Hg. Patients were also excluded if their primary care physician judged, on the basis of risk factors for stroke and haemorrhage, that the patient either should or should not be on warfarin. Thus, random allocation of participants to treatments was ethical, because inclusion was restricted to patients for whom there was clinical uncertainty as to which of the two treatments should be used. Patients with confirmed atrial fibrillation whom the primary care physician judged to be potentially eligible were invited to attend a randomisation clinic for allocation of treatment.

Consent was a two-stage process. An information sheet that explained the aim of the trial and the potential risks and benefits of warfarin versus aspirin in this age group was sent to patients with their invitation to attend a randomisation clinic. At the clinic, the primary care physician went through the information sheet with the patient, and obtained their written informed consent to take part. Randomisation was stratified into six groups on the basis of sex and age (75–79, 80–84, and 85+ years). Within each stratum, randomly permuted

blocks of eight were generated to produce allocation tables that were held by the Birmingham Cancer Trials Unit, which primary care physicians telephoned for the treatment allocation when they had an eligible patient. The study was approved by the West Midlands Multi-centre Research Ethics Committee (MREC/99/7/57).

Procedures

Patients assigned aspirin were prescribed 75 mg daily. Patients assigned warfarin were treated with a target INR of 2·5, with an acceptable range of 2–3, in line with standard UK policy.[30] The frequency or method of INR testing was not altered by the study protocol, which was intended to test real-life control of INR. There are three components to the INR testing: where the blood is taken; where the blood is analysed; and who is responsible for adjusting the warfarin dose. Different general practices undertake none, some, or all of these activities; for those that do none, the patients attend a hospital-based anticoagulation clinic. Frequency of INR testing ranged from once per week or less, if control needed to be established, to every 12 weeks, if the INR were stable.[30] If a patient already being treated with warfarin was randomly assigned to aspirin, then the warfarin therapy was stopped, and vice versa.

The primary outcome was first occurrence of fatal or non-fatal disabling stroke (ischaemic or haemorrhagic), other intracranial haemorrhage, or clinically significant arterial embolism. A stroke was defined by clinical symptoms that developed rapidly, or by signs of focal or widespread loss of cerebral function with symptoms that lasted for more than 24 h or led to death, and had no apparent cause other than one of vascular origin. A disabling stroke was defined by a modified Rankin score of 2–5 at 1 month or longer after stroke, or deterioration in the score if the baseline Rankin score was greater than or equal to 2.[31] A modified Rankin score of 2 is defined as a slight disability, in which the individual cannot undertake all previous activities, but can look after their own affairs without assistance. A stroke that led to a hospital admission of 30 days or more was also classified as disabling. A stroke was classified as fatal if, in the opinion of the endpoint committee, the stroke initiated a sequence of events that led to death. If a death certificate specified stroke but the endpoint committee judged that there was insufficient corroborative clinical information, then the death was not classified as being due to stroke. Classification as intracranial haemorrhage required verification through brain imaging. An arterial embolism was defined as clinically significant if the diagnosis had been confirmed by vascular imaging, scintigraphy, surgery, or autopsy. Pulmonary embolism was not included. Clinical details on possible primary events (ie, clinical notes, discharge summaries, post-mortem reports, results of brain imaging, and death certificate, as applicable) were sent to two independent neurologists who were blind to treatment allocation. They determined whether a primary endpoint had occurred and, if this were a stroke, whether it was ischaemic or haemorrhagic.

	n (%)
Did not meet inclusion criteria	224 (6·1%)
Rheumatic heart disease	53
History of major haemorrhage	53
History of intracranial haemorrhage	30
Active peptic ulcer	12
Oesophageal varices	1
Allergy to study drugs	13
Blood pressure >180/110 mm Hg	15
Recent surgery	8
No longer had atrial fibrillation	18
Terminal illness	19
Wrong age	2
One treatment judged to be beneficial	1995 (54·4%)
Needs warfarin	1570
Should not be on warfarin	417
Specialist referral	8
Patient decision	905 (24·7%)
Wanted to be on warfarin	120
Did not want to be on warfarin	338
Did not want to be on aspirin	11
Did not want to take part in research	409
Did not attend	27
Died or moved away	110 (3·0%)
No reason given	432 (11·8%)
Total	3666

Table 1: **Reasons why patients identified with atrial fibrillation did not take part in the study**

Secondary outcomes were major extracranial haemorrhage (defined as a fatal haemorrhage, or one that resulted in the need for transfusion or surgery), other admissions to hospital for haemorrhage, hospital admission or death as a result of a non-stroke vascular event, and all-cause mortality. Clinical details on possible secondary events were sent to an independent geriatrician blind to treatment allocation, to determine whether a secondary event had occurred.

Primary care physicians reviewed patients every 6 months after treatment allocation, and copies of patients' primary care records were reviewed by researchers between these visits. Use of other risk-modifying treatments (eg, agents to lower blood pressure or blood lipid concentrations) and whether the patient was still taking the trial drugs were monitored. Patients were sent yearly postal questionnaires, and all were flagged with the UK National Health Service Central Register to ensure that BAFTA researchers would be notified of all deaths. For patients whose warfarin treatment was managed in hospital clinics, INR records were obtained from the relevant hospital. Follow-up ceased in September, 2006, at the planned termination of the research funding.

	Warfarin	Aspirin
Number of patients	488	485
Age (years)	81·5 (4·3)	81·5 (4·2)
Age group		
75–79	197 (40%)	200 (41%)
80–84	196 (40%)	190 (39%)
≥85	95 (19%)	95 (20%)
Male	267 (55%)	264 (54%)
Method of identification		
Practice register	342 (70%)	341 (70%)
Screening	146 (30%)	144 (30%)
CHADS2 score*		
1–2	349 (72%)	349 (72%)
3–6	139 (28%)	136 (28%)
On warfarin	194 (40%)	187 (39%)
On aspirin	203 (42%)	204 (42%)
History of stroke or TIA	64 (13%)	60 (12%)
History of hypertension	259 (53%)	269 (55%)
Systolic BP (mm Hg)	139·9 (19·2)	141·3 (19·9)
Diastolic BP (mm Hg)	78·1 (11·1)	78·9 (12·5)
Systolic BP (mm Hg)		
≤160	426 (87%)	408 (84%)
>160	62 (13%)	77 (16%)
Diabetes mellitus	68 (14%)	61 (13%)
Heart failure	96 (20%)	94 (19%)
Myocardial infarction	47 (10%)	56 (12%)
Angina	80 (16%)	75 (15%)

Data are number (%) or mean (SD). TIA=transient ischaemic attack. BP=blood pressure. *A risk stratification scheme for atrial fibrillation. A score of 0–6 is derived based on the following factors: congestive heart failure (1 point); hypertension (1 point); age ≥75 years (1 point); diabetes mellitus (1 point); and previous stroke or TIA (2 points).

Table 2: **Baseline characteristics of patients subsequently treated with warfarin or aspirin**

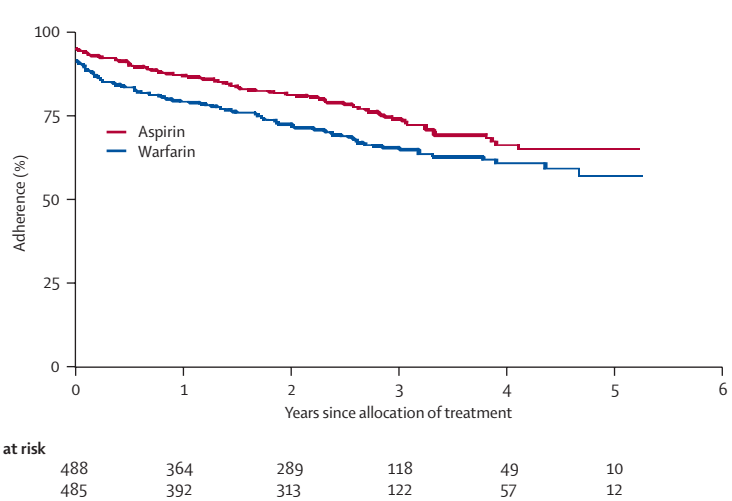

Figure 2: **Kaplan-Meier plot of adherence to allocated treatment**

Statistical analysis

We estimated that a sample size of 1240 patients followed up for an average of 3 years would lead to detection of a 33% difference in the relative risk (RR) of the primary endpoint with 90% power at 5% significance. This assumed a 9% yearly risk of stroke in patients using aspirin,[32] a loss-to-follow-up rate of 1% per year, and a 14% yearly rate of primary endpoints or death. The study was powered on the basis of its primary endpoint alone, not on the basis of the prespecified subgroup analyses or secondary outcomes. Because the frequency of major haemorrhage is lower than the risk of stroke in the age-group used in this study, and any differential effect on other vascular events and all-cause mortality is likely to be small,[8] we recognised that the study would be underpowered to detect differences in secondary outcomes.

The primary analysis was an intention-to-treat comparison of warfarin versus aspirin for prevention of the primary endpoint and of the secondary outcome measures, including major haemorrhage. We calculated RR of yearly event rates and their corresponding 95% CI using the Poisson exact method[33] with SAS version 9.1 and Stata version 9.2. For all analyses, patients were censored at the time of the first event relevant to that analysis—thus, although a patient might have had multiple events, only the first event was counted in each calculation. Hazard ratios were also computed with the log-rank method. These ratios gave the same results as the RR, so are not reported. Subgroup analyses were prespecified for age, method of identification of atrial fibrillation (screening versus case-note review), previous stroke or transient ischaemic attack (TIA), use of warfarin before study entry, and baseline risk of stroke (congestive heart failure, hypertension, age of 75 years or over, diabetes mellitus, and previous stroke or TIA [CHADS2] score 1–2 or 3–5).[34] Kaplan-Meier curves were constructed for the primary event, and to show adherence with study drugs. An on-treatment analysis was prespecified to explore the risks of major haemorrhage (intracranial haemorrhage, including haemorrhagic stroke, or extracranial haemorrhage that was fatal or led to a need for transfusion or surgery). For this analysis, risks were computed according to treatment received. Thus, a patient who switched treatments would contribute exposure time to both warfarin and to aspirin. We did not include time that a patient did not take warfarin or an antiplatelet agent, or any events that occurred during this time. We calculated the RR of a major haemorrhage and its 95% CI using the Poisson exact method. INR control was monitored by the percentage of time spent within the therapeutic range.[35] During the study, interim data were monitored by an independent data and safety monitoring committee; this committee would have halted the trial if a difference of three or more SDs was recorded for a major outcome (terms of reference are available from the corresponding author on request). This study is registered as an

International Standard Randomised Controlled Trial, number ISRCTN89345269.

Role of the funding source

The Medical Research Council had an observer on the trial steering committee, but had no direct role in study design, in data collection, analysis or interpretation, in writing the report, or in the decision to submit for publication.

Results

Figure 1 shows the trial profile. 3231 (70%) of the 4639 patients confirmed to have atrial fibrillation were identified because their primary care records featured atrial fibrillation, and the other 1408 (30%) were identified because they had an irregular pulse in opportunistic screening. Of the whole cohort, 973 (21%) people entered the study. These patients came from 234 of the 260 participating practices; the number of patients recruited per practice ranged from 1 (53 practices) to 21 (1 practice). Of the 181 practices that randomly assigned more than one patient to treatment, 152 allocated at least one patient to each arm of the trial. Table 1 shows the reasons why people did not take part. Over half the exclusions occurred because the primary care physician judged that one treatment would be more beneficial than the other (in most cases, warfarin was preferred).

66 people did not take their allocated drug (figure 1). The most common reason for not taking allocated warfarin was patient reluctance. 35 of the patients who did not take warfarin took aspirin instead, two took clopidogrel, and six took no antithrombotics. Participants were in the study for on average 2·7 years (SD 1·2). Vital status was known at the study end date for all patients apart from two, who had emigrated.

Table 2 shows the baseline patient characteristics. The patients taking warfarin before the study were of similar ages to those not on warfarin (mean age 81·1 *vs* 81·7 years), but had more risk factors for stroke (133 [35%] *vs* 142 [24%] had a CHADS2 score of 3–6).

Figure 2 shows adherence to study therapy. Of 488 patients allocated to warfarin, 326 (67%) remained on this treatment throughout their time in the study. Of those who stopped taking warfarin or did not start taking it, most (127, 78%) were put on an antiplatelet agent (aspirin in 124 cases, clopidogrel in three). Patients on warfarin had INR values in the therapeutic range (2–3) 67% of the time, and were below range 19% and above range 14% of the time. The median INR was 2·3 (IQR 2·0–2·8), and the mean INR was 2·4 (SD 0·84). Of the 234 practices that entered at least one patient for randomisation, 190 allocated at least one patient to warfarin therapy. For 41 (22%) of these practices, the blood taking, INR analysis, and warfarin dosing was done entirely at the hospital; for 58 (30%), the INR analysis and dosing were done at the hospital but the blood was taken at the practice. 47 (25%) practices that allocated at least one patient to warfarin were responsible for all three stages of INR testing, and 36 (19%) were responsible for blood taking and dose adjustment, but the INR was analysed at a hospital laboratory. Eight practices (4%) did not report how they monitored the INR. Of patients allocated to aspirin, 368 (76%) remained on this drug the whole time they were in the study. However, 82 (70%) of those who stopped taking aspirin (or did not start that treatment) were switched to or stayed on warfarin.

There were no differences in blood pressure or in use of lipid-lowering therapy between treatment allocation groups after randomisation. For example, 2 years after randomisation, 96 patients (25%) assigned to warfarin and 86 patients (23%) assigned to aspirin were on a lipid-lowering agent. The mean systolic blood pressure at this time was 137 mm Hg (SD 20) for patients on warfarin

	Warfarin (n=488)		Aspirin (n=485)		Warfarin *vs* aspirin	
	n	Risk per year	n	Risk per year	RR (95% CI)	p
Stroke	21	1·6%	44	3·4%	0·46 (0·26–0·79)	0·003
By severity						
Fatal	13	1·0%	21	1·6%	0·59 (0·27–1·24)	0·14
Disabling non-fatal	8	0·6%	23	1·8%	0·33 (0·13–0·77)	0·005
Type of stroke*						
Ischaemic	10	0·8%	32	2·5%	0·30 (0·13–0·63)	0·0004
Haemorrhagic	6	0·5%	5	0·4%	1·15 (0·29–4·77)	0·83
Unknown	5	0·4%	7	0·5%	0·69 (0·17–2·51)	0·53
Other intracranial haemorrhage†	2	0·2%	1	0·1%	1·92 (0·10–113·3)	0·65
Systemic embolism‡	1	0·1%	3	0·2%	0·32 (0·01–3·99)	0·36
Total number of events	24	1·8%	48	3·8%	0·48 (0·28–0·80)	0·0027

RR=relative risk. *Type of stroke was determined by the endpoint committee on the basis of brain imaging or post-mortem findings. If neither of these was available, the stroke was classified as unknown. †The three other intracranial haemorrhages were subdural; two of these were fatal (one in each treatment group). ‡Two of the systemic emboli were fatal (one in each treatment group).

Table 3: **Nature of primary events**

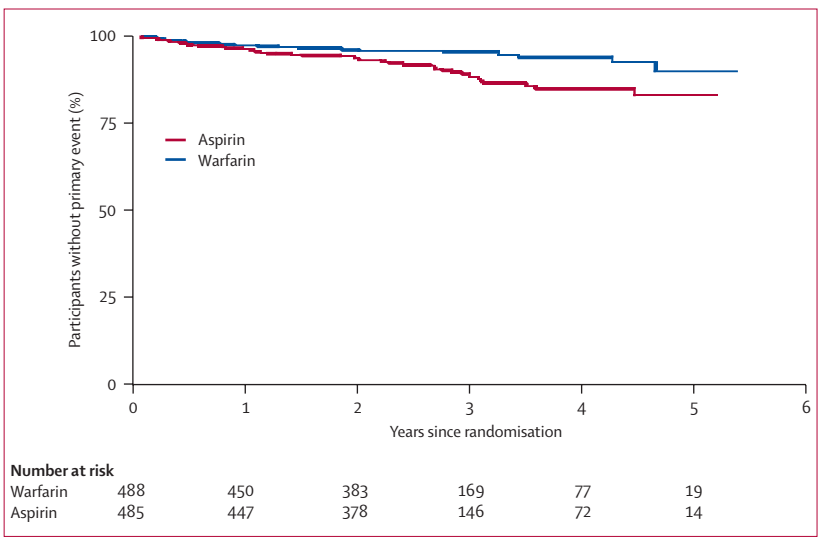

Figure 3: **Kaplan-Meier plot of time to primary event**

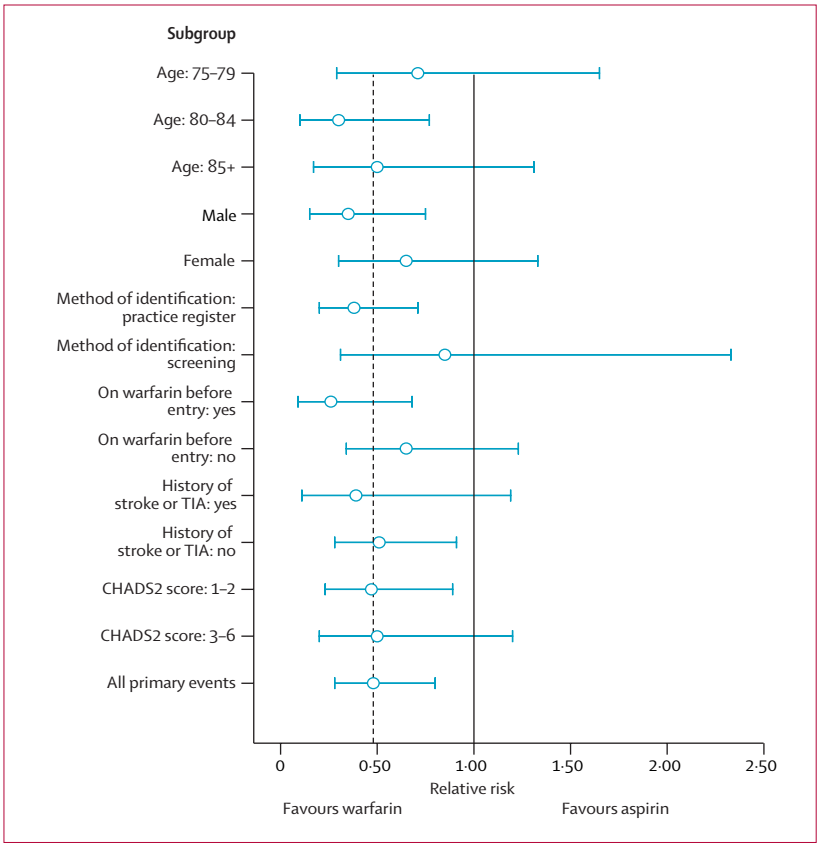

Figure 4: **Relative risk of all primary events by subgroup**
Bars show the 95% CIs calculated by Poisson exact method. The broken line shows relative risk of primary events in the whole trial population. TIA=transient ischaemic attack.

or aspirin, and the mean diastolic blood pressure was 75 (11) mm Hg for patients on warfarin and 76 (11) mm Hg for patients on aspirin.

There were fewer primary events in patients assigned to warfarin than in those assigned to aspirin (24, 1·8% per year *vs* 48, 3·8% per year, RR 0·48, 95% CI 0·28–0·80) (table 3, figure 3). We used these results to calculate the number needed to treat for one year to prevent one primary event as 50.

Risk of stroke rose with age, was particularly high in people who had already had a stroke or TIA, was higher in people already known to have atrial fibrillation than in those identified by opportunistic screening, and was higher in people on warfarin before study entry than in those new to this treatment (figure 4, table 4). There was no evidence of an interaction between the effectiveness of warfarin and any of these patient subgroups. In particular, warfarin was as effective in people aged 85 years or over as it was in younger people.

We also compared the effect of warfarin with that of aspirin on risk of major haemorrhage in these subgroups, but CIs are wide because there were only 50 events (table 4). There were no significant interactions. Yearly risk of haemorrhage did not differ between people assigned to warfarin who were on anticoagulant therapy at study entry and those who were not. Risks of bleeding rose by similar amounts with age in both groups.

Table 5 shows secondary outcomes. Warfarin was no better than aspirin at prevention of non-stroke vascular events, and overall mortality rates were the same in both groups. The composite outcome of major vascular events (ie, stroke, myocardial infarction, pulmonary embolus, or vascular death) was slightly lower in people on warfarin than in people on aspirin. The risk of admission to hospital with any non-stroke vascular event did not differ between the treatment groups.

There was no evidence of increased risk of a major haemorrhage (ie, an intracranial haemorrhage, or one that was fatal or resulted in the need for transfusion or surgery) in patients on warfarin compared with those on aspirin (table 5). The net benefit therefore favoured oral anticoagulation. The on-treatment analysis for major haemorrhage similarly identified no difference between warfarin and aspirin (RR 0·88, 95% CI 0·46–1·63).

Discussion

We have shown that warfarin is more effective than aspirin in prevention of stroke in people with atrial fibrillation who are aged 75 or over. With respect to our primary aim, we showed that the frequency of major stroke, arterial embolism, and intracranial haemorrhage was significantly lower in patients on warfarin than in those on aspirin. With respect to our secondary aims, we recorded no evidence that anticoagulants were more hazardous than aspirin therapy in this age-group, although the study had limited power to detect those differences. Nevertheless, the rate of major haemorrhage on warfarin was gratifyingly low in this primary care setting. We also recorded no difference in all-cause mortality or in other vascular events, but the CIs were not sufficiently narrow to enable us to be certain that warfarin had no effect.

We showed a significant result for the primary endpoint despite the lower-than-predicted event rates and study size. This finding indicates the benefit of warfarin over aspirin for stroke prevention. Figure 5 compares our results with an individual-patient data meta-analysis[8] of warfarin versus aspirin from subgroups of patients within the same age-group as used in BAFTA. The effect on stroke prevention was of a similar magnitude in BAFTA as in the meta-analysis. The yearly risk of a major bleed in people on aspirin was similar in the two data sets: 1·5% in the meta-analysis and 2·0% in BAFTA. The key difference between the two sets of results is that the meta-analysis reported a doubling of risk of major haemorrhage in people on oral anticoagulants compared with those on aspirin, whereas we showed no such difference, even though we used a low dose (75 mg) of aspirin. If we had used a larger dose of aspirin, the frequency of bleeding in this group might have been even higher.[36]

	Primary event						Major haemorrhage*					
	Warfarin		Aspirin		Warfarin *vs* aspirin		Warfarin		Aspirin		Warfarin *vs* aspirin	
	n/N	Risk per year	n/N	Risk per year	RR (95% CI)	p†	n/N	Risk per year	n/N	Risk per year	RR (95% CI)	p†
Sex												
Male	10/267	1·4%	27/264	3·9%	0·35 (0·15–0·75)	0·23	13/267	1·8%	14/264	2·1%	0·89 (0·39–2·04)	0·74
Female	14/221	2·3%	21/221	3·5%	0·65 (0·30–1·33)	..	12/221	2·0%	11/221	1·9%	1·06 (0·43–2·65)	..
Age												
75–79	11/197	2·0%	15/200	2·8%	0·71 (0·29–1·65)	0·57	6/197	1·1%	4/200	0·8%	1·44 (0·34–6·95)	0·53
80–84	6/196	1·1%	19/190	3·8%	0·30 (0·10–0·77)	0·45	12/196	2·3%	12/190	2·4%	0·96 (0·39–2·33)	0·80
85+‡	7/95	2·8%	14/95	5·6%	0·50 (0·17–1·31)	..	7/95	2·9%	9/95	3·7%	0·77 (0·24–2·32)	..
Method of identification§												
Practice register	15/342	1·7%	38/341	4·5%	0·38 (0·20–0·71)	0·16	18/342	2·1%	16/341	1·9%	1·10 (0·53–2·31)	0·51
Screening	9/146	2·0%	10/144	2·3%	0·85 (0·31–2·33)	..	7/146	1·5%	9/144	2·1%	0·73 (0·23–2·21)	..
On warfarin before entry												
Yes	6/194	1·4%	21/187	5·1%	0·26 (0·09–0·68)	0·10	7/194	1·6%	10/187	2·5%	0·65 (0·21–1·89)	0·32
No	18/294	2·0%	27/298	3·1%	0·65 (0·34–1·23)	..	18/294	2·1%	15/298	1·8%	1·18 (0·56–2·51)	..
History of stroke or TIA												
Yes	5/64	3·1%	12/60	8·0%	0·39 (0·11–1·19)	0·66	1/64	0·6%	5/60	3·4%	0·18 (0·004–1·65)	0·10
No	19/424	1·6%	36/425	3·2%	0·51 (0·28– 0·91)	..	24/424	2·1%	20/425	1·8%	1·17 (0·62–2·22)	..
CHADS2 score¶												
1–2	15/349	1·5%	31/349	3·3%	0·47 (0·23–0·89)	0·85	19/349	2·0%	16/349	1·7%	1·15 (0·56–2·40)	0·33
3–6	9/139	2·5%	17/136	5·0%	0·50 (0·20–1·20)	..	6/139	1·7%	9/136	2·7%	0·63 (0·19–1·99)	..

*Major haemorrhage was defined as extracranial bleeds that were fatal or required transfusion or surgery, or intracranial haemorrhage (including haemorrhagic stroke). †p values are for interactions between treatments and subgroups (ie, whether the treatment has different effects in different groups). ‡Interaction reference category. §Patients identified through practice registers were already known to have atrial fibrillation; patients identified through screening were mostly newly identified as having atrial fibrillation. ¶See footnote to table 2 for explanation of CHADS2 score.

Table 4: **Risk of primary event and major haemorrhage by treatment allocation for different patient subgroups**

	Warfarin		Aspirin		Warfarin *vs* aspirin	
	N	Risk per year	N	Risk per year	RR (95% CI)	p
Death						
All causes	107	8·0%	108	8·4%	0·95 (0·72–1·26)	0·73
Fatal primary endpoint	15	1·1%	23	1·8%	0·63 (0·31–1·26)	0·16
Other vascular death*	41	3·1%	34	2·7%	1·16 (0·72–1·88)	0·53
Non-vascular death*	51	3·8%	51	4·0%	0·96 (0·64–1·45)	0·84
Secondary vascular outcomes (fatal and non-fatal)						
All strokes	33	2·5%	61	4·9%	0·52 (0·33–0·80)	0·002
All strokes plus TIA	40	3·1%	70	5·7%	0·55 (0·36–0·82)	0·002
Myocardial infarction	15	1·1%	15	1·2%	0·96 (0·44–2·11)	0·91
Heart failure	38	2·9%	23	1·8%	1·59 (0·92–2·79)	0·08
Other vascular events†	34	2·6%	45	3·7%	0·71 (0·44–1·13)	0·13
All non-stroke vascular events	78	6·1%	76	6·3%	0·97 (0·70–1·35)	0·84
Haemorrhage (fatal and non-fatal)						
Major extracranial haemorrhage	18	1·4%	20	1·6%	0·87 (0·43–1·73)	0·67
Other hospital admission for haemorrhage	24	1·8%	19	1·5%	1·22 (0·64–2·36)	0·52
All major haemorrhages (including intracranial and haemorrhagic stroke)	25	1·9%	25	2·0%	0·96 (0·53–1·75)	0·90
Composite outcomes						
Major vascular events (stroke, myocardial infarction, pulmonary embolus,‡ vascular death)	76	5·9%	100	8·1%	0·73 (0·53–0·99)	0·03
Primary events plus major haemorrhage	39	3·0%	64	5·1%	0·59 (0·38–0·89)	0·008

Analyses are censored at first event, so the composite outcomes are not the sum of the individual categories of event. *Includes deaths that occurred after non-fatal primary endpoints, including four deaths from stroke (as 'other vascular death'). †Other events leading to hospital admission or death, such as angina, deep vein thrombosis, acute bowel ischaemia, pulmonary embolism, acute arrhythmia, and elective vascular surgery. ‡There were five pulmonary emboli, one in the warfarin group and four in the aspirin group.

Table 5: **Risk of secondary and composite outcomes by treatment allocation for different patient subgroups**

The similarity in risk of major haemorrhage between patients on warfarin and those on aspirin in this study is surprising. There are several possible explanations. First, the CIs for our estimate of risk of major haemorrhage were wide, so we cannot exclude the possibility that warfarin does increase risk compared with aspirin. However, if warfarin does increase the risk, it does so by less than the twofold increase estimated in the meta-analysis of individual-patient data.[8] Second, some of the anticoagulation trials that were used for the meta-analysis had higher target INR ranges than BAFTA: the upper end of the range was 4·5 in SPAF II,[18] 4·2 in AFASAK,[20] and 4·0 in the European Atrial Fibrillation Trial,[37] compared with the BAFTA target of 2·5 (acceptable range 2–3). Risk of intracranial bleeding is much higher in patients who have an INR greater than 4.[38] Notably, the beneficial effects on stroke prevention in BAFTA were similar to those in the meta-analysis, in which the mean INR target was higher.[8] A further possible explanation for the low occurrence of bleeding in people on anticoagulation therapy in BAFTA is that 40% of patients were on warfarin before entry to the study, since the hazards of warfarin seem to be greater in people who are new to the treatment. In ACTIVE W,[13] the yearly risk of a major haemorrhage was 2·0% in people randomly assigned to warfarin who were already on the drug, compared with 2·9% in people who were started on warfarin as part of the trial. (In the studies used for the meta-analysis, patients were all new to anticoagulation.[8]) However, we did not record significant differences in haemorrhage risk between people who were naive to warfarin and those who had previously been on the treatment (2·1% *vs* 1·6%). Importantly, the degree of INR control in our study resembles the control in typical primary care practice in the UK, and thus is likely to show the true hazard of warfarin in non-trial settings. Indeed, a cohort study of 27 Scottish practices reported that INR control was in the target range (2–3) 68% of the time—very similar to our control.[28] The degree of INR control achieved in this study was similar to that in other trials that have aimed for a target INR of 2–3. Patients on warfarin were within the target INR range for 64% of the time in ACTIVE W, and for 61% of the time in SPAF III.[13,32]

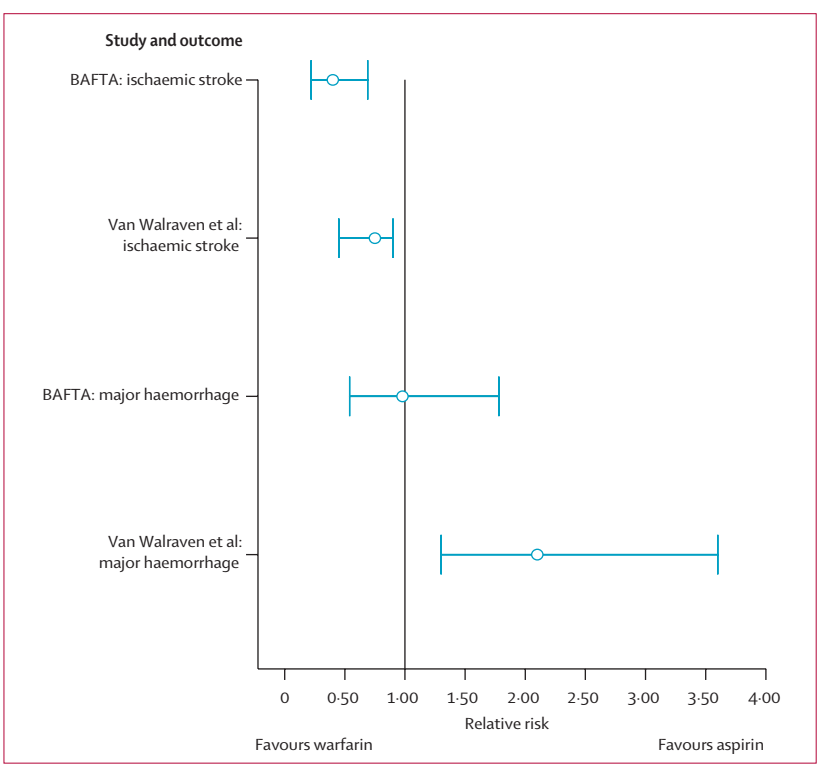

Figure 5: **Indirect comparison of results from BAFTA for ischaemic stroke and major haemorrhage with results from six other randomised trials of aspirin versus anticoagulation**
BAFTA results are compared with those from a meta-analysis by Van Walraven and colleagues[8] that used data from individual patients aged ≥75 years from six previous studies.

The low safety of aspirin in this age-group was also seen in the Warfarin Versus Aspirin for Stroke Prevention in Octogenarians with Atrial Fibrillation trial. This trial randomly assigned 75 patients aged 80–90 years to warfarin or aspirin, and reported a higher rate of side-effects and intolerance to aspirin (albeit at the higher dose of 300 mg per day) than to warfarin.[39] Furthermore, people with atrial fibrillation in the ACTIVE W trial who were randomly assigned to anticoagulation therapy with a target INR of 2–3 or to aspirin plus clopidogrel had a similar yearly risk of haemorrhage (2·2% on oral anticoagulation *vs* 2·4% on the antiplatelet combination).[13]

Another possible explanation for the absence of difference in bleeding risk between warfarin and aspirin is the crossover between treatment. A third of people randomly assigned to warfarin did not start the treatment or started it but later stopped, and 17% of patients randomly assigned to aspirin were taking warfarin by the end of the study. These crossovers are likely to dilute differences in effect between the agents. Thus, although we have probably underestimated the benefit of warfarin over aspirin in prevention of ischaemic stroke and thromboembolism, the crossovers might also have led to underestimation of bleeding risk, if people perceived to be at high risk of haemorrhage were taken off warfarin. However, the effect is likely to be small, because no differences were reported in either the intention-to-treat or the on-treatment analyses.

The slightly greater number of hospital admissions for heart failure in the warfarin group is probably a chance finding. The difference was not significant, and admission for heart failure was one of multiple secondary outcomes that were tested. Other vascular and all-cause mortality did not differ between the warfarin and aspirin groups. This finding might be because of low power, but is consistent with the meta-analysis of the oral anticoagulant versus aspirin trials,[8] which reported hazard ratios of 0·95 for vascular death and 0·93 for all-cause death at all ages. Only 20% of deaths in BAFTA were attributable to fatal primary endpoints or subsequent fatal strokes, so the efficacy of warfarin on stroke risk

reduction is diluted by the 80% of deaths not related to stroke. The apparent absence of difference between warfarin and aspirin with respect to other vascular events might be due to the similar effectiveness of aspirin and warfarin in prevention of these events.[40]

We recorded no significant differences in risk of primary event or major haemorrhage in the different patient subgroups that we looked at. However, the study was not powered to detect interactions, so these analyses might be thought of as only exploratory, particularly for the risk of major haemorrhage, for which there were few events.

Warfarin was associated with a lower risk of primary endpoint than aspirin for all age-groups, and there was no evidence that the risks of warfarin relative to aspirin increased with age. Indeed, in people aged 85 years or over, the risk of a major haemorrhage was 27% lower on warfarin than it was on aspirin (this difference was not significant). Nevertheless, the yearly risks of major haemorrhage rose with age for both treatments, being on average over 3% in people aged 85 years or over. We did not allocate a group to no treatment in this study, so we do not know what the risk of major haemorrhage in this age-group would have been without treatment.

An advantage of a study based on primary care, such as BAFTA, is that the nature of the interventions are as close as possible to the real clinical situation. Furthermore, the results are related to the effectiveness of the treatments in the general population, by contrast with studies that recruit from hospital settings, where patients might be atypical.[41] Nevertheless, only 21% of the study population that we identified as having atrial fibrillation took part in the study; we estimate that this is about 10% of the total study population of people over the age of 75 years who had atrial fibrillation, because only about half of people we identified as potentially having atrial fibrillation responded to an initial invitation to attend the practice for a study ECG.[42] This recruitment rate is similar to that in other atrial fibrillation trials that attempted to identify the total study population. For example, the SPAF trial included 7% of patients identified in atrial fibrillation.[43] The primary-care-based studies AFASAK1 and AFASAK2 recruited respectively 40% and 24% of patients who attended an ECG laboratory and had an ECG showing atrial fibrillation.[20,22] In the primary-care-based Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation study, 21% of identified patients were randomly assigned to a trial that involved treatment with anticoagulants.[21]

Do these low proportions of the total population affect the applicability of the findings? In BAFTA, the most common reason provided for exclusion of patients was a clinical preference for anticoagulation. This finding suggests that the effect of the patient selection was to underestimate the potential benefit of anticoagulation, because these patients are likely to have been those in whom anticoagulation was perceived to be safer, and in whom the risk of stroke was likely to be higher. Indeed, the risk of stroke in patients randomly assigned to aspirin was higher in BAFTA in people on warfarin at entry to the study than in people who were not on warfarin. Few patients were excluded because of perceived high risk of haemorrhage: only 20% of the patients excluded because the treatments were not judged to have equal potential benefit were excluded because warfarin was felt to be inappropriate. Interestingly, patients were more likely to state a preference not to be on warfarin than one to be on it, but these preferences might change as a result of the data made available by this trial.

In this study, strokes needed to be of the most clinically severe types (fatal or disabling) to qualify as a primary endpoint. Therefore, the recorded benefits are in terms of prevention of serious clinical events. We probably did not capture all the minor strokes and TIAs that occurred. This is a possible explanation for the higher proportion of fatal strokes reported in this study than in ACTIVE W,[13] although our proportion of fatal strokes was similar to that in the Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation III trial.[44]

For the BAFTA study, we used 75 mg aspirin, the dose most commonly used in the UK for stroke prevention in patients with atrial fibrillation. There is strong evidence that this dose is at least as effective as higher doses for stroke prevention for indications other than atrial fibrillation,[45] and the risk reduction for stroke achieved by aspirin in atrial fibrillation is of the same order of magnitude as is achieved in other high-risk groups.[5,45] There is no evidence that different aspirin doses have different effects in the atrial fibrillation trials,[7] so a higher dose of aspirin in this study would probably not have been any more effective at preventing stroke, whereas as it would have been likely to increase haemorrhage rates.[36]

The primary event rate in BAFTA was lower than we had anticipated, especially in patients with additional risk factors for stroke. For example, people on aspirin with a CHADS2 score of 3–6 had a yearly risk of a primary event of only 3·3%, compared with an anticipated average risk nearer to 9%.[34] Lower than anticipated event rates were also reported in ACTIVE W.[13] These lower rates are probably caused by a decline in the frequency of stroke secondary to unrelated changes in management of other risk factors, such as blood pressure and blood cholesterol.[4] The low rates also mean that the benefit of warfarin over aspirin in terms of absolute risk reduction is low—2% per year. Nevertheless, more primary events were recorded in people with a history of stroke or TIA, confirming the importance of this as a risk factor for stroke in atrial fibrillation, as emphasised in guidelines for England and Wales.[25]

We might have underestimated the benefits of anticoagulant therapy compared with aspirin in the elderly population as a whole, because many patients at high risk of stroke will have been excluded from the study

and because of the treatment crossovers. Studies have reported that only 46% of people with atrial fibrillation over the age of 75 years with a history of stroke or TIA were on warfarin in primary care,[26] and that less than half of people aged over 75 years with atrial fibrillation were discharged from hospital on warfarin.[27] Our results show that warfarin could safely be used much more widely in this age-group. In summary, these data lend support to the use of anticoagulation for all people aged over 75 years who have atrial fibrillation, unless there are contraindications or the patient decides that the size of the benefit is not worth the inconvenience of the treatment.[46] The target INR should be 2–3—a range in which there is clear evidence of benefit and no evidence from this study of harm compared with aspirin. Age itself should not be regarded as a contraindication to anticoagulation therapy.

Contributors

JM, FDRH, DF, and GYHL participated in conception of the study, and JM, FDRH, DF, EM, and GYHL designed the study. KF contributed to amendments to study design. JM, FDRH, and KF were responsible for data acquisition. JM, KF, and AR were responsible for data analysis, and JM, FDRH, KF, AR, and GYHL were responsible for data interpretation. JM wrote the first draft of the paper, and all authors contributed to subsequent drafts. All authors have seen and approved the final version.

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Conflict of interest statement

GYHL has received funding for research, educational symposia, consultancy, and lecturing from manufacturers of drugs used to treat atrial fibrillation and thrombosis (AstraZeneca, Sanofi-Aventis, Bayer, Astellas, and Daiichi-Sanko). GYHL was clinical advisor to the Guideline Development Group that wrote the UK National Institute for Health and Clinical Excellence guidelines on management of atrial fibrillation, and is on the writing committee for the American College of Chest Physicians guidelines on antithrombotic therapy for atrial fibrillation. All other authors declare that they have no conflict of interest.

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