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Study protocol

Protocol for Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA): a randomised controlled trial of warfarin versus aspirin for stroke prevention in the management of atrial fibrillation in an elderly primary care population [ISRCTN89345269]

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Abstract

Background: Atrial fibrillation (AF) is an important independent risk factor for stroke. Randomised controlled trials have shown that this risk can be reduced substantially by treatment with warfarin or more modestly by treatment with aspirin. Existing trial data for the effectiveness of warfarin are drawn largely from studies in selected secondary care populations that under-represent the elderly.

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study will provide evidence of the risks and benefits of warfarin versus aspirin for the prevention of stroke for older people with AF in a primary care setting.

Study design: A randomised controlled trial where older patients with AF are randomised to receive adjusted dose warfarin or aspirin. Patients will be followed up at three months post-randomisation, then at six monthly intervals there after for an average of three years by their general practitioner. Patients will also receive an annual health questionnaire.

1240 patients will be recruited from over 200 practices in England. Patients must be aged 75 years or over and have AF. Patients will be excluded if they have a history of any of the following conditions: rheumatic heart disease; major non-traumatic haemorrhage; intra-cranial haemorrhage; oesophageal varices; active endoscopically proven peptic ulcer disease; allergic hypersensitivity to warfarin or aspirin; or terminal illness. Patients will also be excluded if the GP considers that there are clinical reasons to treat a patient with warfarin in preference to aspirin (or vice versa).

The primary end-point is fatal or non-fatal disabling stroke (ischaemic or haemorrhagic) or significant arterial embolism. Secondary outcomes include major extra-cranial haemorrhage, death (all cause, vascular), hospital admissions (all cause, vascular), cognition, quality of life, disability and compliance with study medication.

Background

Atrial fibrillation (AF) is associated with a 50% to 90% increase in all cause mortality, principally due to excess risk of death from cardiovascular diseases including stroke [1,2]. It is a particularly important risk factor for stroke in the elderly, since both the incidence of stroke and the prevalence of AF rise with age [3,4]. Whilst AF is associated with 15% of all strokes, it is associated with 36% of strokes in people over the age of 80 [5]. It is important, therefore, to identify the most effective strategy for stroke prevention for older people with AF.

Four major strategies have been tested in clinical trials to reduce stroke risk in AF including the use of: adjusted-dose warfarin; anti-platelet agents such as aspirin; fixed low dose warfarin and fixed low dose warfarin in combination with aspirin. Previous studies have shown that both fixed low dose warfarin and the combination of low dose warfarin with aspirin are significantly less effective than adjusted dose warfarin. [6–9] The principal alternatives to reduce stroke risk in patients with AF are therefore adjusted dose warfarin or aspirin.

There is strong evidence that adjusted dose warfarin is highly effective in reducing risk of stroke and thromboembolism in people with non-rheumatic AF [10–12]. A meta-analysis of five trials of warfarin therapy suggested that this approach results in a 68% reduction in risk of stroke [10]. An important side effect of warfarin is haemorrhage, but under trial conditions, observed rates of serious haemorrhage have been low [10]. Aspirin appears to be a safer, but less effective alternative to warfarin resulting in a 22% reduction in risk of stroke [12,13].

A summary of the seven trials which have directly compared antiplatelet agents to warfarin for stroke prevention in AF in the relevant age group (where possible) is shown in table 1. While three studies [6,14,15] found significant benefits of adjusted dose warfarin over aspirin of the order of magnitude that would be anticipated from the indirect comparisons, these findings were not replicated in the other four studies. Indeed, two of the studies showed non-significant results in favour of aspirin [8,16]. Published meta-analyses of the trials have reached different conclusions due, in part, to controversy [17] as to which trials should be included in this review [12,18]. Notwithstanding this issue, study populations of trials examining the use of warfarin for patients in AF significantly under-represented elderly people. In excess of 50% of people in AF in the community would be expected to be over the age of 75,[4] whilst only 20% of patients in the trials were in this age group [10]. In the EAFT study, age was the main reason patients were considered ineligible for the study, accounting for 55% of exclusions [14]. As a result, the evidence for the effectiveness of warfarin in AF for patients

over the age of 75 is much less impressive than the evidence for patients under this age [19]. Sub-group analysis of a review of five trials suggested that warfarin did reduce stroke risk in this age group, but it was based on only 24 events [10].

There are also concerns over the safety, in terms of increased haemorrhagic risk, of warfarin [18] and this may be particularly important for older age groups. In the SPAF II study, the annual risk of stroke with residual deficit (haemorrhagic and ischaemic) was in fact slightly higher (4.6% vs 4.3%) in patients aged over 75 assigned to warfarin as opposed to aspirin [16]. Factors that might increase risk of major haemorrhage in very elderly patients on warfarin include: deficits in auditory and visual acuity; risk of falls; impaired cognition and memory; dietary vitamin K deficiency; polypharmacy; amyloid angiopathy; and occult gastro-intestinal lesions [19]. A secondary analysis of the SPAF trial data, comparing adjusted dose warfarin versus aspirin, found age to be an important risk factor for major haemorrhage on warfarin [20]. This association of age with risk of haemorrhage has been found in some observational studies,[21,22] but not others [23].

Finally, it is important that a trial performed to investigate the role of anticoagulation in the elderly is carried out in a primary care setting [24]. The existing evidence base for the benefits of anticoagulation is comprised of trials that were mostly conducted on hospital populations. General practitioners (GPs) have questioned the applicability of the results of these studies to primary care settings [25]. Patients were mostly recruited from hospital, and 3% to 40% of patients identified with AF were entered into the trials. While many exclusions were legitimate (e.g. prior indication for warfarin, or clear contra-indication), some were less justifiable (for example about a third of patients in the SPAF II study were excluded for reasons that may have related to perceived haemorrhage risk). It is noteworthy that concerns over risk of haemorrhage were found to be the main barrier to anticoagulant use by primary care physicians in the USA [26]. If GPs assume that the risks of haemorrhage in their practice are higher than was observed in the trials, the perceived harm/benefit ratio for individual patients is changed. Therefore, to improve the likelihood that results of the proposed study are acted upon, it is important that it is carried out in a setting which is representative of primary care [24].

Overall, the limitations of the evidence base for management of AF in elderly primary care population is reflected in low uptake of anticoagulation in clinical practice. Audits of use of warfarin in AF have consistently demonstrated low uptake of the therapy, particularly in the elderly. Recent studies based in defined UK general practice

Table 1: Randomised controlled trials which have compared aspirin with adjusted dose warfarin in the treatment of atrial fibrillation

Study	Population	Age	Interventions	Primary end-point	Relative risk of primary end-point (95% CI)
AFASAK I [15].	Primary care. N = 671 (in relevant arms)	No age limits. Mean age 74 yrs.	3 arm study including warfarin (INR 2.8–4.2) and aspirin (75 mg).	Stroke, transient ischaemic attack and systemic embolus.	Not given. RR on warfarin as compared to aspirin or placebo: 0.36
EAFT [14].	TIA or minor stroke in preceding 3/12 N = 455 (in relevant arms)	65% were >69 yrs	3 arm study, including anti-coagulant (INR 2.5–4.0) and aspirin (300 mg).	Death from vascular disease; non-fatal stroke (including haemorrhage); non-fatal myocardial infarction or systemic embolus	0.60 (0.41 to 0.87)
SPAF II [16].	N = 385	>75 yrs	Warfarin (INR 2.0–4.5) vs aspirin (325 mg).	Ischaemic stroke and systemic embolus	0.73 (0.37 to 1.5) 1.07 (stroke with residual deficit including haemorrhagic)
AFASAK II [8].	Primary care. N = 339 (in relevant arms)	No upper age limit. Mean age 73 yrs.	3 arm study, including warfarin (INR 2.0–3.0) and aspirin (300 mg) arms.	Stroke (ischaemic or haemorrhagic) or systemic thrombo-embolus.	1.26 (intention to treat) 0.78 (treatment received analysis)
SIFA [43].	Recent cerebral ischaemia N = 916	Age > 30 yrs Mean age 72 yrs.	Warfarin (INR 2.0–3.5) vs indobufen (200 mg bd or 100 mg bd if creatinine clearance < 80 mls/min).	Stroke (including haemorrhagic), myocardial infarction, pulmonary embolus, systemic embolus or vascular death	0.85 (not significant)
SPAF III [6].	At least 1 risk factor for stroke N = 1044	No upper age limit. Mean age 71 yrs.	Warfarin (INR 2.0–3.0) vs aspirin (325 mg) and fixed mini-dose warfarin (INR 1.2–1.5).	Ischaemic stroke and systemic embolus	0.26 (0.13 to 0.50)
PATAF [9].	Primary care. N = 272 (in relevant arms)	Age 60–78. Mean age 70 yrs.	3 arm study including warfarin (INR 2.5–3.5) and aspirin (150 mg).	Stroke, systemic embolus, major haemorrhage or vascular death.	0.78 (0.34 to 1.8)

[In the relative risk column, the risk of an end-point on variable dose warfarin is compared to the risk on aspirin (and fixed-minidose warfarin in the case of SPAF-III). Thus, a relative risk greater than one favours aspirin, and a relative risk less than one favours warfarin]

populations have found that only between 18% and 40% of people in AF without contra-indications for therapy were being treated with warfarin. [27–29] Sudlow *et al* found that only 17% of patients in AF over the age of 74 were on warfarin [30]. There is also no clinical consensus with regard to use of anticoagulation in the elderly. In a review of the content of guidelines on anticoagulant treatment in AF in Great Britain, Thomson *et al* found that between 13% and 100% of patients with AF would be treated depending upon which guideline was used [31]. An important cause of this variation was different advice with regard to age. Ten of 20 guidelines referred to the higher risks of anticoagulation in the elderly, and eight gave upper age limits, with four recommending not treating people over the age of 80, and two suggesting that anticoagulation should be used in people over the age of 75 only in exceptional circumstances. If, as is current practice, the majority of patients over the age of 75 with AF are not treated with warfarin, targeting this group of patients is likely to have a substantial public health benefit in

terms of preventing stroke [32] if warfarin is indeed more effective than aspirin.

In conclusion, although there is a good evidence basis to support adjusted-dose warfarin as the most effective strategy for the prevention of stroke in AF, there are limitations when applying these data to older people (75 years or over) and a trial focusing on this age group is needed [19]. The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) aims to provide robust data on the effectiveness, in terms of stroke prevention and haemorrhagic risk, of adjusted dose warfarin versus aspirin in older patients with AF identified from primary care settings.

Methods
Study Aims
The primary aim of BAFTA is to compare the incidence of fatal and non-fatal disabling stroke (ischaemic or haemorrhagic) and systemic embolism in older patients with AF who are treated with either adjusted dose warfarin or aspirin.

Study design and setting

BAFTA is a primary-care based, pragmatic randomised controlled trial where older people (aged 75 years or over) with AF are randomised to receive either warfarin or aspirin. The pathway by which patients are recruited is given in figure 1. A full economic evaluation is also being conducted.

Ethical considerations

Full ethical approval for this study has been obtained. Two external bodies, a Data Monitoring and Ethics Committee and a Trial Steering Committee, will monitor study progress.

Study interventions

Adjusted dose warfarin with a target international normalised ratio (INR) of 2.5 (acceptable range of 2.0 to 3.0) was selected as this is the recommended strategy of the British Society of Haematology for the treatment of AF [33]. Warfarin dosage and INR monitoring may be carried out in primary care or hospital clinics, depending on whichever is the standard procedure for the participating practice. Methods for adjusting warfarin dose and monitoring INR are at the discretion of the local practices and hospital anticoagulation clinics. Patients allocated aspirin will receive 75 mg daily as this dose has been shown to be as effective as higher doses (e.g. 300 mg) in the prevention of stroke [34].

Identification of eligible patients

Eligible patients will be identified from general practices in England selected mainly from the West Midlands. Larger practices (three or more partners) will be recruited in preference to smaller ones. Each practice will receive a start-up visit by a member of the research team who will run a practice-based computer search to identify all patients aged 74 years or over. Within this population, patients with probable AF will be identified in three ways: by computerised searches of GP records; by opportunistic screening of the pulse by practice staff and by considering patients who present with previously undiagnosed AF ('incident cases').

The computerised note searches of general practice records will be tailored towards the information held in each practice and will identify patients who have already been diagnosed as having AF. Patients in this group will be invited to attend an ECG clinic at their practice. The opportunistic screening will take place by placing a flag (paper or computerised) in the case notes of all patients aged 74 years or over who were not identified as being in AF as a result of the computer searching. The flag prompts a member of the primary health care team to take the patient's pulse the next time the patient consults. It is anticipated that over 12 months, 91% of patients in this age range will have been seen at least once by their GP [35]. Pulse palpation is a highly sensitive (though non-specific) way of detecting AF (sensitivity = 94%) [36]. The result of the pulse check (regular or irregular) is recorded and those patients with an irregular pulse will be invited to an ECG clinic.

Confirmation of diagnosis of AF: the ECG clinic

The practice nurse records a 12 lead ECG and collects other baseline information (table 3) at a dedicated clinic. The ECG is sent to the study team to be read by a cardiologist, who will report whether AF is present or absent and list any other significant abnormalities. Where the ECG shows sinus rhythm, but the patient has a case note diagnosis of AF, records of ECGs and relevant case notes over the previous two years will be reviewed. If there is evidence of chronic atrial fibrillation (permanent or paroxysmal) in the case records, including evidence of at least one ECG in the last two years showing AF, then this patient will be considered eligible. Cases where the AF appears transient or self-limiting are excluded. Patients identified as an incident case, who had an ECG outside the BAFTA study, will have this ECG submitted to the BAFTA cardiologists for reading and do not need to be called to the dedicated nurse clinic.

Determining eligibility for the study

Eligibility for the study is determined in two stages. Firstly, the practice nurse, in consultation with the GP, reviews the patient's medical records to check whether the patient satisfies the study inclusion criteria and does not have any of the absolute exclusion criteria listed in table 2. Secondly, the GP decides whether there is clinical uncertainty as to whether the patient should be treated with aspirin or warfarin, taking into account other clinical factors (see table 2, and randomisation clinic below). Eligible patients are invited to a randomisation clinic appointment. All patients will have received a detailed information sheet about the BAFTA study before their randomisation clinic appointment. Patients who are not eligible for a randomisation clinic appointment are followed-up at the GP's discretion.

Randomisation clinic

At the randomisation clinic the GP once again checks to ensure that the patient satisfies both inclusion and absolute exclusion criteria. Patients with temporary exclusion criteria (table 2) are not eligible for the study, though may be re-considered at a later date.

The decision as to whether or not the patient is eligible for trial entry is made by the GP using the uncertainty principle. That is, if a GP is certain that a patient should not be entered into the trial, for whatever reason, that patient is not eligible for entry into BAFTA. If the GP is substantially
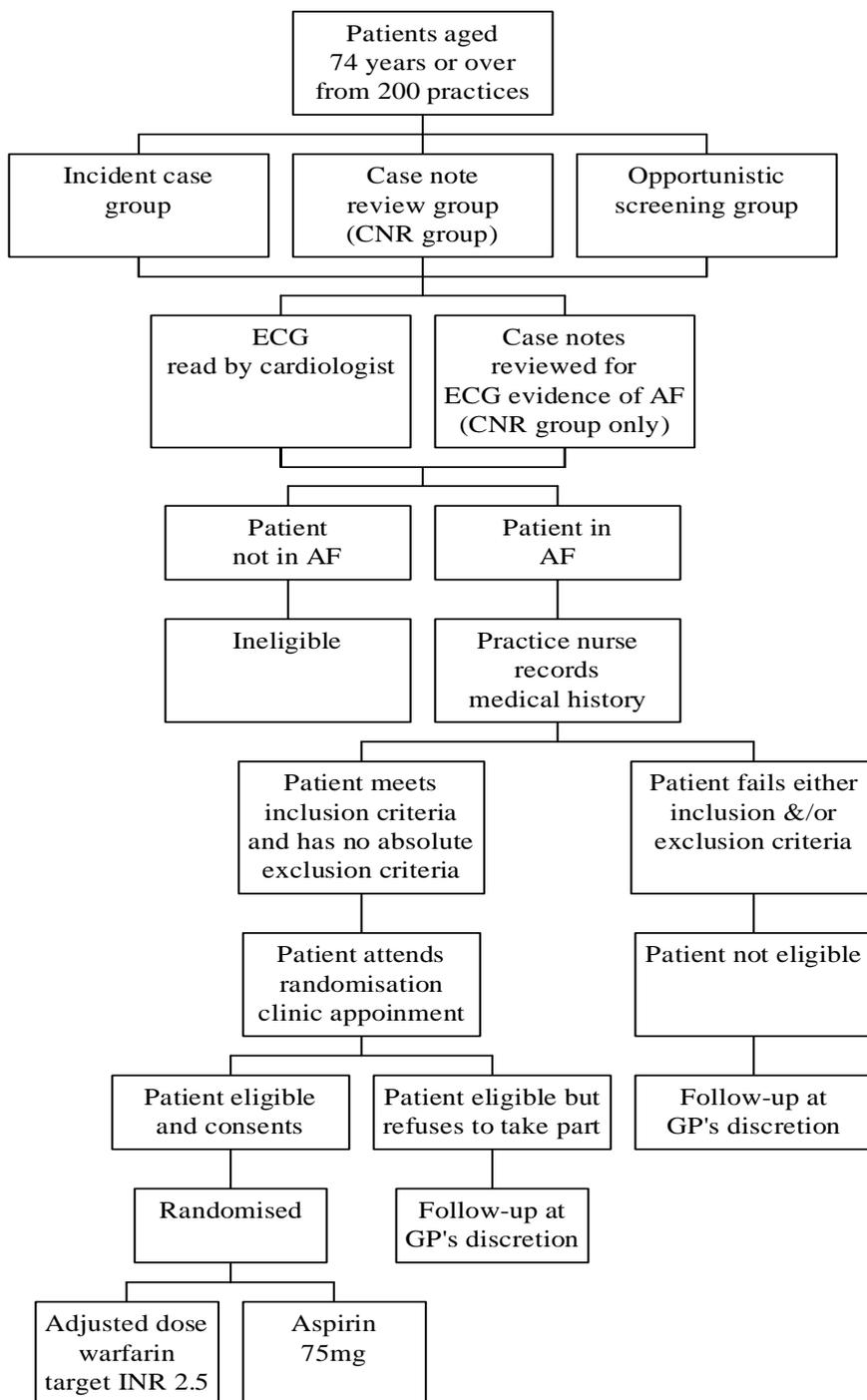
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                    ┌─────────────────────┐
                    │   Patients aged     │
                    │  74 years or over   │
                    │  from 200 practices │
                    └─────────────────────┘

┌──────────────┐    ┌──────────────┐    ┌──────────────┐
│ Incident case│    │  Case note   │    │ Opportunistic│
│    group     │    │ review group │    │  screening   │
│              │    │ (CNR group)  │    │    group     │
└──────────────┘    └──────────────┘    └──────────────┘

         ┌──────────────┐    ┌──────────────┐
         │     ECG      │    │  Case notes  │
         │ read by      │    │  reviewed for│
         │ cardiologist │    │ ECG evidence │
         │              │    │  of AF       │
         │              │    │ (CNR group   │
         │              │    │   only)      │
         └──────────────┘    └──────────────┘

         ┌──────────────┐    ┌──────────────┐
         │   Patient    │    │  Patient in  │
         │  not in AF   │    │     AF       │
         └──────────────┘    └──────────────┘

         ┌──────────────┐    ┌──────────────┐
         │  Ineligible  │    │Practice nurse│
         │              │    │   records    │
         │              │    │medical history│
         └──────────────┘    └──────────────┘

   ┌──────────────┐         ┌──────────────┐
   │Patient meets │         │Patient fails │
   │  inclusion   │         │either        │
   │ criteria     │         │inclusion &/or│
   │ and has no   │         │exclusion     │
   │  absolute    │         │  criteria    │
   │exclusion     │         │              │
   │ criteria     │         │              │
   └──────────────┘         └──────────────┘

   ┌──────────────┐         ┌──────────────┐
   │Patient attends│        │Patient not   │
   │randomisation │         │  eligible    │
   │clinic        │         │              │
   │ appoinment   │         │              │
   └──────────────┘         └──────────────┘

┌───────────┐ ┌───────────┐ ┌──────────────┐
│ Patient   │ │ Patient   │ │  Follow-up at│
│ eligible  │ │eligible but│ │GP's discretion│
│and consents│ │refuses to │ │              │
│           │ │take part  │ │              │
└───────────┘ └───────────┘ └──────────────┘

┌───────────┐ ┌───────────┐
│Randomised │ │Follow-up at│
│           │ │GP's        │
│           │ │discretion  │
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┌───────────┐ ┌───────────┐
│Adjusted   │ │ Aspirin   │
│dose       │ │  75mg     │
│warfarin   │ │           │
│target INR │ │           │
│  2.5      │ │           │
└───────────┘ └───────────┘
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Figure 1
Summary of trial design. Incident case group: *patient presents with atrial fibrillation to GP;* Case note review group: *patient is identified through GP computer system;* Opportunistic screening group: *patient is identified through opportunistic taking of pulse.*

Table 2: Study inclusion and exclusion criteria

Inclusion criteria
• Aged 75 years or over.
• Atrial fibrillation or flutter confirmed by a study ECG or ECG taken within 2 years of the practice start-up visit.
Absolute exclusion criteria
• Rheumatic heart disease.
• Major non-traumatic haemorrhage (e.g. gastro-intestinal).
• Intra-cranial haemorrhage.
• Oesophageal varices.
• Endoscopically proven peptic ulcer disease in previous year.
• Known allergic hypersensitivity to either of the study medications.
• Patient is known to be terminally ill.
Temporary exclusion criteria
• Uncontrolled hypertension (BP > 180 systolic or 110 diastolic). In such circumstances, the patient will be eligible once the hypertension has been brought under control.
• Recent surgery or head injury (i.e. in last three months). In such circumstances, patient will be eligible once three months had elapsed.
Other relevant factors
1. Poor memory / cognitive function which is defined here as a score of 10 or more on the short orientation-memory concentration test [37]. If the patient does not 'pass' this test, but has a carer who is responsible for the patient's medication, then they are eligible for the trial.
2. Alcohol dependency (30 units per week or more) or binge drinking (10 units at a time).
3. Poorly controlled epilepsy such that the patient is at significant risk of head injury.
4. Risk of falls likely to result in head injury.
5. Long term use of non-steroidal anti-inflammatory agents (NSAIDs). In this circumstance, patients who are on NSAIDs with a lower risk of gastro-intestinal haemorrhage such as ibuprofen, diclofenac or naproxen [40]. are eligible. Given the risks associated with the long term use of NSAID therapy in older age people with atrial fibrillation, consideration should be given to changing patients to alternative medication, and then reviewing trial eligibility.
6. Factors known to increase risk of stroke in these patients: previous stroke or transient ischaemic attack, known heart failure, systolic BP greater than 150 mmHg or diabetes.

uncertain whether or not warfarin is indicated, then the patient is eligible for BAFTA. This decision will need to be made on a case by case basis after consideration of all relevant factors listed in table 2. Patients already on warfarin or aspirin are eligible for consideration. In each case, factors which increase risk of haemorrhage (points 1 to 5) need to be set against the high risk of stroke in these patients, which is increased still further by certain factors (point 6). If the GP remains uncertain as to whether or not the patient should be on warfarin or aspirin, the patient will be offered trial entry. Patients with substantial cognitive impairments (defined as 10 or more on the Short Orientation Memory Concentration test [37] or 8–9 at the GP's discretion) can be considered for trial entry as long as a carer from the patient's family is willing to support the patient's entry into the trial, and the GP is satisfied that warfarin could be safely administered.

If the patient (and carer where appropriate) is willing to take part, the GP then obtains written consent from the patient (and carer) prior to randomisation. The randomisation will be stratified by age into three strata (75–79; 80–84; and 85+) with gender balanced by minimisation. The randomisation schedule has been developed by an independent trials unit, and the random allocation is obtained by GPs telephoning this randomisation service. Once the treatment allocation has been obtained, the GP

then prescribes the trial medication and arranges the appropriate clinical follow up. Patients who are either ineligible for trial entry or who do not wish to take part in the study are treated at the discretion of the GP.

Patient follow-up procedures
Patients will be followed up from trial entry until the end of the study (anticipated average: three years). Follow-up is composed of several elements. First, at three months post-randomisation and then six monthly intervals there afterwards, the GP will review each patient and record evidence of any primary or secondary end-points (listed in table 3) and compliance with trial medication. Second, at six monthly intervals but three months after the GP review, a researcher will review the patient's medical records and note whether or not primary and secondary outcomes have occurred. Third, at twelve months post-randomisation and annually there afterwards the patient will be sent a postal health questionnaire (described in table 3). Non-responders will be sent a second questionnaire within three weeks, and then contacted by telephone if they fail to respond after two successive mailings. The records of patients will be flagged at the NHS Central Register to ensure that the study team is informed about any deaths that occur. Finally, INR data for patients on warfarin will be obtained from their hospital or GP records.

Table 3: Timing and content of study assessments

Identifying eligible patients: Baseline data

ECG clinic: practice nurse interview-administered schedule
• *Socio-demographic characteristics*:
Age, sex and ethnicity.
• *Medical history*:
Previous history of hypertension, stroke, transient ischaemic attack, diabetes, myocardial infarction, heart failure, angina, rheumatic fever, valvular heart disease, oesophageal varices, peptic ulcer disease or intra-cranial haemorrhage. Current prescription medications. Smoking status and alcohol intake.
• *Clinical measures*:
Blood pressure and a 12 lead ECG.
Receipt of ECG results: practice nurse & GP review of the medical record
• *Medical history (for patients in atrial fibrillation only)*:
Previous history of hypertension, stroke, transient ischaemic attack, diabetes; myocardial infarction, heart failure, angina, rheumatic fever, valvular heart disease, oesophageal varices, peptic ulcer disease or intra-cranial haemorrhage. Current prescription medications.
Randomisation clinic
Patient schedule: self-completion
• Disability assessed by the Rankin Score [3].
• Health related quality of life assessed by the SF-12 [41] and EQ-5D. [38].
Practice nurse schedule: interview
• Blood pressure, current prescription medications and the Short-Orientation Memory Concentration test [37].
GP schedule: interview
• Review of inclusion and exclusion criteria and record outcome of consent process.

Patient follow-up procedures: for an average of three years

Obtaining information on patients who died
• Records flagged at NHS central register.
GP interviews at 3 months post-randomisation, then six monthly intervals there afterward
• Major extra-cranial haemorrhage (fatal, or one that requires transfusion or surgery).
• Death – all cause, all vascular and stroke.
• Admission to hospital – all cause, all vascular, stroke.
• Cognition assessed by Mini-Mental State Exam [42]. at (9, 21, and 33 month follow-ups only).
• Disability assessed by the patient using the Rankin Score [3].
• Blood pressure and apical pulse rate.
• Drop out/withdrawal from allocated medication.
Researcher case note review at 6 months post-randomisation, then six monthly intervals there afterward
• Major extra-cranial haemorrhage (fatal, or one that requires transfusion or surgery).
• Death – all cause, all vascular and stroke.
• Admission to hospital – all cause, all vascular, stroke.
• Drop out/withdrawal from allocated medication.
Patient self-completed postal questionnaire at 12 months post-randomisation, then annually there afterwards
• Disability assessed by the Rankin Score [3].
• Health related quality of life assessed by the SF-12 [41] and EQ-5D [38].
• Patient costs questionnaire (warfarin patients only, at 12 months).

Patient outcome measures
The criteria used to assess whether or not the patient is suitable for inclusion in the study, and the primary and secondary outcome measures assessed across the follow-up period for patients randomised are summarised in table 3.

The primary outcome is the incidence of fatal or non-fatal disabling stroke (ischaemic or haemorrhagic), intra-cranial haemorrhage or significant arterial embolism. A disa-

bling stroke is defined as a Rankin Score [3] of 2 to 5 one month or more after stroke, or a deterioration in the score if the baseline Rankin Score was greater than or equal to 2. If the stroke led to a hospital admission of 30 days or more, this is also classified as a disabling stroke. Intra-cranial haemorrhage will require verification through brain imaging and includes sub-dural haemorrhage and sub-arachnoid haemorrhage. Significant arterial embolism also requires verification by vascular imaging, scintigra-

phy, surgery or autopsy. Pulmonary embolism is not included as a primary outcome.

When a possible primary end-point is identified in the study population, the hospital discharge summary, results of brain imaging and a copy of the death certificate (if applicable) will be obtained. These data will be scrutinised by two neurologists independently, blind to the treatment allocation. They will decide whether or not a primary end-point has occurred and classify strokes as thrombo-embolic, haemorrhagic, or uncertain.

A variety of secondary outcome measures are assessed during the GP follow-ups, researcher case note review and the annual patient questionnaire (table 3). Key secondary outcomes include: major extra-cranial haemorrhage (defined as a fatal haemorrhage, or one that requires transfusion or surgery); all stroke (including non-disabling stroke); vascular deaths; all deaths; and vascular admissions (including myocardial infarction and pulmonary embolus). Since the GPs providing clinical care are unblinded, pulse and blood pressure are being monitored to reflect any possible differential treatment in the two groups (for example, better treatment of hypertension or heart failure). Key secondary events (deaths, extracranial major haemorrhage; vascular admissions) will be reviewed by an independent clinician blinded to treatment allocation to ensure unbiased coding of these events.

Sample size considerations

Randomisation of 1240 patients (620 in each arm), with an average of three years follow-up, will detect a 33% reduction in the relative risk of acute stroke (ischaemic or haemorrhagic) or arterial embolus between groups with 90% power (alpha = 0.05). This figure assumes that the annual incidence of the primary end-point on aspirin is 9%,[6,16] the annual rate of primary end-points or death will be 14% and that loss to follow up will be 1%.

To recruit 1240 patients from primary care, an estimate of the number of practices is needed. It was assumed that 7% of the general population are aged 75 years or over and about 9% of this age range will be in AF [4]. Of these, 35% might be expected to have a contra-indication to warfarin [27] and 17% have an indication for warfarin [30]. This suggests that 48% of patients identified as being in AF will be eligible to enter the trial. If 75% of eligible patients are identified, and 50% of these agree to enter the trial, this would result in a recruitment rate of 113 per 100,000 practice population. Therefore, to recruit 1240 patients a total practice population of 1,097,000 is required comprising 76,800 aged 75 years or over. This equates to 157 practices with an average list size of 7,000 and recruitment of eight patients per practice.

Statistical analysis

The primary analysis will be a comparison of warfarin with aspirin for prevention of the primary end-point following the "intention to treat" principle. Intention to treat analyses will also be performed for the secondary outcomes. Analyses of primary and secondary endpoints, comparing time to event in the two arms, will be performed using the log rank method. Cox regression will also be carried out. All significance tests will be two-sided. Pre-planned sub-group analysis will be performed for the following sub-groups: age (75–79, 80–84, 85+ years) and gender; method of identification of AF (opportunistic screening/computer search identified); history of prior stroke or transient ischaemic attack (yes/no); on warfarin prior to study entry (yes/no); and study ECG showing atrial fibrillation or sinus rhythm (as pragmatic distinction between permanent and paroxysmal atrial fibrillation). A secondary on-treatment analysis will be performed to explore the risks of major haemorrhage. We will also explore the possible effects of other patient characteristics such as blood pressure and concomitant use of other nonsteroidals.

Economic evaluation

The economic evaluation will adopt a broad perspective, including costs incurred within the health sector and by patients and carers. Data collection will be undertaken on all trial patients in order to allow a stochastic cost analysis to be conducted. The focus of the data collection will be upon the key cost drivers which will include: drug and INR monitoring, contacts with secondary care; primary care visits. The analysis will adopt an incremental approach such that data collection will concentrate on resource use differences between trial arms. The process of collecting data on resource use will be undertaken separately from data collection on unit costs. Resource use data will principally be collected within the trial. Unit costs will be collected from published sources and a representative sample of NHS providers in order to increase generalisability. The methods to be used in collecting data will include a review of patient records (both GP and hospital), whilst private costs data will be collected from a survey of a sub-cohort of the trial population.

Plan of analysis

It is not possible to state with certainty at the outset which form of economic analysis will be employed, since this will be driven in part by the trial results. The plan for the analysis is to report a cost consequence analysis, which will involve providing a full description of all important results relating to costs and consequences. If no differences in consequences are observed, then a cost minimisation analysis will be conducted. If differences in consequences are observed, then a cost utility analysis will be conducted using data on EQ-5D [38] to estimate Qual-

ity Adjusted Life Years. Whichever form of analysis is employed, an incremental approach will be used. To predict overall programme costs, the mean costs per patient will be compared using either parametric or non-parametric methods depending on the distribution of the data [39].

Longer term costs and consequences will be explored by extrapolating beyond the end of the trial using a modelling framework. The precise form of modelling is yet to be determined, but is likely to be either Markov or Discrete Event Simulation, depending upon the extent to which the Markov assumptions are justified. An advantage of using such an approach is that it will allow the additional costs of increasing survival to be explicitly incorporated into the analysis.

The robustness of the results of the economic analysis will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings. Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by estimating cost-effectiveness acceptability curves. These plot the probability that the intervention is cost-effective against threshold values for cost-effectiveness.

Time plan for the BAFTA study
Patient recruitment began in April 2001 and is planned to continue until December 2004. By August 2003, 382 patients (31% of target) have been recruited into the trial.

Competing interests
None of the authors have any competing interests arising from this research.

Contributions of authors
Jonathan Mant, Richard Hobbs, David Fitzmaurice, Gregory YH Lip, Ellen Murray, Teresa Allan, Stirling Bryan and James Raftery were responsible for identifying the research question, and contributing to drafting of the study protocol. Suzanne Richards, Miriam Banting, Kate Fletcher and Joy Rahman have all contributed to the development of the protocol and study design, as members of the research team. Jonathan Mant and Suzanne Richards were responsible for the drafting of this paper, although all authors provided comments on the drafts and have read and approved the final version.

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