The safety and adequacy of antithrombotic therapy for atrial fibrillation:
a regional cohort study

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ABSTRACT

Background
Atrial fibrillation is a common problem in older people. The evidence base for the safety of warfarin and aspirin in atrial fibrillation is largely derived from selective research studies and secondary care. Further assessment of the safety of warfarin in older people with atrial fibrillation in routine primary care is needed.

Aim
To measure the complication rates and adequacy of warfarin control in a cohort of patients with atrial fibrillation managed in primary care and compare them with published data from controlled trials and community patients with atrial fibrillation not receiving warfarin.

Design of study
Retrospective review of regional cohort.

Setting
Twenty-seven general practices in southwest Scotland.

Method
Case note review of 601 patients previously identified as having atrial fibrillation by GPs.

Results
The average age of our cohort was 77 years at recruitment. Two hundred and sixty-four (44%) patients died within 5 years of follow up. Three hundred and nine of the 601 (51%) patients with atrial fibrillation took warfarin at some stage during this study. INR (international normalised ratio) was maintained between 2 and 3 for 68% of the time. Bleeding risk was higher in patients taking warfarin than in those on aspirin or no antithrombotic therapy (warfarin 9.0% per year versus aspirin 4.7% per year versus no therapy 4.6% per year). The annual risk of any bleeding complication on warfarin (9%) was similar to that recorded in randomised trials (9.2%) whereas the annual risk of severe bleeding was approximately double (2.6 versus 1.3%).

Conclusion
Adequacy of anticoagulant control was broadly comparable to that reported in clinical trials, whereas the risk of severe bleeding was higher, possibly reflecting the older age and the comorbidities of our unselected cohort.

Keywords
anticoagulation; antithrombotic therapy; atrial fibrillation; cohort study.

INTRODUCTION

Since the publication of a series of trials[1,2] in the mid-1990s, demonstrating that warfarin was more effective than aspirin in preventing strokes for patients with atrial fibrillation, there has been concern that the results of research were not readily applicable to routine practice.[3] In particular a difference in age and comorbidity between trial and routine populations, the adequacy of anticoagulation management in primary care, and the complication rate are legitimate areas for examination.

Several studies have demonstrated that patients in routine practice are older and have more comorbidity than those in the major trials.[4–7] More recently evidence from hospital outpatients has been used to suggest that stroke and complication rates in practice are comparable to those seen in the studies.[8] The use of warfarin has increased over the last 10 years.[9] Studies of mixed populations of warfarin users show that structured anticoagulation care in primary care is comparable to that in specialist practice[10] and that age,[11] possibly mediated through dependency,[12] increases the risk of bleeding.

Our study aimed to compare the complication rates and adequacy of warfarin control in a cohort of patients with atrial fibrillation managed in primary care with published data from controlled trials.

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How this fits in

Many patients with atrial fibrillation in primary care are older and have more comorbidity that those in trials of warfarin. Age has little effect on adequacy of international normalised ration control for patients prescribed warfarin for atrial fibrillation by their GPs. Major bleeding complication rates are higher in routine practice than in trials, but this applies to patients prescribed warfarin, aspirin or neither. Total bleeding complication rates with warfarin appear similar to those in trials.

METHOD

The study used existing general practice records. Practices identified patients from a regional audit of atrial fibrillation carried out in 1996 and, after checking for deaths and incorrect diagnoses of atrial fibrillation, invited surviving patients, by letter, to have their data reviewed. Ethical approval was obtained for an opt-out method of consent in order to obtain comprehensive patient coverage. We limited the study sample to patients with persistent atrial fibrillation (as opposed to atrial fibrillation, which was either paroxysmal or transient in the context of other illness) in the original cohort who were alive on 1 January 1999 and reviewed clinical records from 1 April 1998 (to allow between 4 and 5 years of follow up) to the time of data collection or death.

Data on living patients were collected by a research nurse who visited practices between July 2002 and March 2003 and manually extracted data from paper and computer records. The notes of patients who had died after 1 January 1999 were reviewed in a similar process at the record storage facility of NHS Scotland. Records of patients identified in 1996, but who had died before 1 January 1999, had been destroyed under data handling policies.

The data comprised baseline patient characteristics (age, sex and significant comorbidity); antithrombotic therapy (with separate entries for each period of treatment if this changed during the follow-up period); strokes and bleeding events (allowing multiple entries per patient). For nearly all the patients on warfarin, an additional dataset (comprising up to 2 years of consecutive INR [international normalised ratio] results) was drawn from the records. All blood tests were analysed in the hospital laboratory, with samples taken and dosing managed by the GP practice. Computerised dosing support was not widely used at the time of the study.

Bleeding events were defined as episodes of internal or external bleeding or bruising necessitating consultation and documented in contemporaneous practice records or hospital correspondence. We did not examine any systems for routine checking about bleeding on warfarin. We categorised such events as severe where there was evidence of death, intracranial bleeding or hospital admission within 24 hours.

Antithrombotic therapy was coded as warfarin, antiplatelet or neither. At baseline, 18 (7.9%) of patients taking warfarin were also taking aspirin. Because of their small number this group was analysed with those on warfarin alone. Patients on no antithrombotic therapy included both those who had never had aspirin or warfarin and those whose treatment had been stopped. Where bleeding events and strokes occurred between the issue dates of prescriptions by the practice they were assumed to occur on the earlier treatment.

The diagnosis of stroke was based on the hospital discharge or clinic letter where available and GP records if the patient was not referred for specialist assessment. To verify the data on stroke and intracranial bleeding we reviewed all cranial CT scan reports on study patients from the single district general hospital serving the population.

Statistical methods

The composition of the cohort by age (<75 and ≥75 years) and treatment at recruitment (warfarin, aspirin, or no antithrombotic therapy) and prior stroke (yes/no) was tabulated, as well as the rate of strokes, bleeding complications, and death per patient year, expressed as a percentage.

The number of bleeding events and the observed patient years in the study period were counted, and the rate per patient year (expressed as a percentage) calculated, both overall and by subgroups of treatment, age, severity and organ system. A similar analysis was performed for incidence of new stroke (fatal and non-fatal) and all causes death. In addition, for all causes death only odds ratios (ORs) for aspirin and warfarin in comparison with no treatment were calculated. This was not carried out for other analyses as subjects were not limited to one event.

Adequacy of anticoagulation control with warfarin[13] was summarised by the time spent in range and the mean INR. Time spent in range was calculated using Rosendaal's method of linear interpolation,[14] with a target therapeutic INR range of 2–3. INR data from the eight patients with six or less INR readings were excluded from the analysis. For those who had a bleed on warfarin with an INR reading at the time of, or immediately preceding the bleed, the OR comparing INR >3 with the rest was calculated.

Among those that had strokes, the number of subjects with a fatal stroke was compared in the subgroup of those aged ≥75 years and on no antithrombotic therapy with the rest.

All analyses were performed using SPSS for Windows 11.0 and SAS 8.2 for Windows (SAS Institute, Cary, NC, US). No adjustments have been made for multiple comparisons.

RESULTS

Completeness of data collection

Twenty-seven of the 28 practices in the original audit took part in this study and casenotes were reviewed for 601 patients (307 males and 294 females) with persistent atrial fibrillation. Of the 1120 patients in the audit, 226 could not be traced, and 293 were known to have died prior to 1 January 1999.

The average age of the current cohort was 77 years. One hundred and thirty-three (22%) patients had experienced a stroke or transient ischaemic attack before the start of the study period. Warfarin was taken by 309 (51%) patients with atrial fibrillation at some stage during the study. There were 264 (44%) patients who died within up to 5 years of follow up. These and other baseline data are summarised in Table 1.

INR data

INR data was obtained from 259 of the 309 patients who took warfarin by reviewing medical records and extracting saved INR results. No INR data were available at the time of casenote review for 50 patients, 40 of whom had died before the data collection. Tests from the 2 most recent years (or less where there was limited data) were recorded from 27 practices yielding 5816 INR readings. The median number of patients with INR data per practice was 10 (range = 1–20).

Incidence of stroke and death

There were 50 new episodes of stroke in 45 (7.4%) patients with a mean age of 80 years at occurrence. Eleven strokes were associated with death within 30 days. A further 14 patients had a non-specific diagnosis of cerebrovascular disease listed as one of their registered causes of death. The diagnosis of stroke was made clinically in all cases and confirmed by CT scan in 22 (44%). Of the 13 strokes occurring while taking warfarin, eight were scanned, four were rated as minor and one was fatal. In all, 264 (44%) patients died during the 4–5 years of follow up. Table 2 shows the rates of stroke and death by age and treatment category. Rates of stroke and all cause mortality were lower among patients receiving warfarin than aspirin or no treatment in both age groups.

Adequacy of anticoagulant control

The effect of age on INR time in range was estimated by pooling all tests for patients aged <75 years (134 patients, 3246 tests) and ≥75 years (111 patients, 2550 tests) of age. There was no clinically important

Table 1. Characteristics of 601 patients with persistent atrial fibrillation.

	Number of patients (%)		
	Aged <75 years	Aged ≥75 years	Total
Number at outset	260	341	601
Stroke or TIA prior to April 1998	52 (20.00)	81 (23.75)	133 (22.13)
Treatment at outset			
Patients without prior stroke or TIA			
Warfarin	99 (47.59)	65 (25.00)	164 (35.04)
Aspirin	57 (27.40)	90 (34.62)	147 (31.41)
No antithrombotic therapy	52 (25.00)	105 (40.3)	157 (33.55)
Patients with prior stroke or TIA			
Warfarin	31 (59.62)	34 (41.98)	65 (48.87)
Aspirin	17 (32.69)	33 (40.74)	50 (37.59)
No antithrombotic therapy	4 (7.69)	14 (17.28)	18 (13.53)
Patient years of follow up			
Warfarin	539 (53.85)	414 (36.60)	953 (44.70)
Aspirin	294 (29.37)	427 (37.75)	721 (33.82)
No antithrombotic therapy[a]	168 (16.78)	290 (25.64)	458 (21.48)
Total	1001	1131	2132
Events (% per patient year)			
Strokes	15 (1.50)	35 (2.83)	50 (2.20)
Bleeding complications	60 (5.99)	81 (7.16)	141 (6.61)
Deaths	72 (7.19)	191 (16.89)	263 (12.34)

[a]*For patients on no antithrombotic therapy, 216 patient years were for patients never prescribed treatment, and 241 for patients whose treatment had been stopped.*
TIA = transient ischaemic attack.

Table 2. Incidence of new stroke and death by current antithrombotic therapy.

	Aged <75 years			Aged ≥75 years			All patients			
	Nil	Aspirin	Warfarin	Nil	Aspirin	Warfarin	Nil	Aspirin	Warfarin	Total
Patient years	168	294	539	290	427	414	458	721	953	2132
Fatal stroke										
Cases	1	0	1	5	3	1	6	3	2	11
Rate (%)	0.60	0.00	0.19	1.72	0.70	0.24	1.31	0.66	0.28	0.52
All strokes										
Cases	4	4	7	12	17	7	16	21	13	50
Rate (%)	2.98	1.36	1.48	5.86	4.68	1.69	4.80	3.57	1.64	2.35
Death										
Cases	21	25	27	76	71	43	97	96	70	263
Rate (%)	12.50	8.50	5.00	26.20	16.60	10.40	1.20	13.30	7.30	12.34
OR		0.68	0.4		0.63	0.4		0.63	0.35	
95% CI		(0.37 to 1.26)	(0.22 to 0.73)		(0.44 to 0.91)	(0.34 to 0.77)		(0.46 to 0.86)	(0.25 to 0.48)	

Rates calculated as % per patient year, OR calculated versus no treatment. OR = odds ratio.

Table 3. Bleeding events by treatment and age group.

	Aged <75 years			Aged ≥75 years			All patients			
Treatment	Nil	Aspirin	Warfarin	Nil	Aspirin	Warfarin	Nil	Aspirin	Warfarin	Total
Patient years	168	294	539	290	427	414	458	721	953	2132
Severe bleeds										
Events	2	5	15	4	9	10	6	12	25	43
Rate (%)	1.20	1.70	2.80	1.40	2.10	2.40	1.30	1.90	2.60	2.02
All bleeds										
Events	4	12	44	17	22	42	21	34	86	141
Rate (%)	2.40	4.10	8.20	5.90	5.20	10.10	4.60	4.70	9.00	6.61

Severe bleeding event defined as fatal, intracranial or requiring hospital admission. Rates calculated as % per patient year.

Rates of stroke were lower in patients treated with warfarin, as was all cause mortality. The difference in stroke was comparable to that seen in randomised controlled trials. However in this non-randomised study we were unable to differentiate between the direct benefits of warfarin and confounders such as a 'healthy user' effect, whereby GPs selectively prescribed warfarin for their fitter patients. In our earlier study of this cohort we showed that GPs choice of treatment for patients with atrial fibrillation was variably influenced by prognostic factors and that younger patients were more likely to be given warfarin than older patients;[6] this effect persisted in the current study as demonstrated by the different prescribing rates by age group shown in Table 1.

Comparison with existing literature

Study population. Compared to patients included in a recent meta-analysis[1] our cohort was older (mean age 77 versus 73 years), more likely to have a new stroke (4% per patient year versus 1.5%), and much more likely to die during follow up. No fewer than 264/601 (40.9%) patients died during an average of 42 months follow up compared to 252 of the 4498 (5.6%) trial patients dying over an average of 30 months. Our study was also unusual in describing high rates of warfarin and aspirin use (51% took warfarin at some time and only 17% took no antithrombotic therapy throughout the study period). In describing the effects of extrapolating research evidence into clinical practice this study complements both the original trials and more recent surveys of practice, generally hospital based, from the UK,[5–8] Europe,[15–18] Australia[19] and Canada,[20] however none had such an inclusive community sample nor as long a follow-up period. A recent, larger, health maintenance organisation-based study from US[21] used survival analysis to argue that warfarin produced a reduction in stroke rates after adjusting for prognostic factors.

Adequacy of anticoagulation. The measures of quality of anticoagulation control refute the argument that elderly patients with atrial fibrillation might receive anticoagulation at doses too low to be effective.[3] Using recognised measures of quality, results were close to the standard of specialist anticoagulant clinics. For the majority of practices the average INR in target range value was at, or close to the desired level of 70%. Our finding that an INR above 3.0 was associated with a threefold increase in bleeding risk compared to one in the range 1.6–3.0 supports the view that lower levels of anticoagulation may give the best balance between safety and efficacy for older patients with atrial fibrillation.

Bleeding complications. Annual rates of severe bleeding complications on warfarin (2.6%) were higher than in the trials (pooled trials severe bleeding rate 1.3%) but overall bleeding rates were similar (9.0 and 9.2%, respectively). We suspect that our estimate of severe bleeding is likely to be accurate because we used a definition (death, intracranial bleeding or hospital admission) that was easy to verify, but that we will have under estimated minor bleeding on the grounds that GPs were not required to record all cuts, bruises and minor nose bleeds in the patient record.

The incidence of severe bleeding was also high in patients prescribed aspirin or no antithrombotic therapy (1.9 and 1.3%, respectively) suggesting an underlying higher risk in this older population. The relative risk of bleeding on warfarin compared to aspirin was similar to that seen in trials.

Our study showed only a small age-related difference in bleeding risk due to warfarin treatment, with the annual risk of any bleeding being 8.2% for patients aged <75 years and 10.1% for those ≥75 years.

Although many of the bleeding episodes were not dangerous, even relatively modest bleeds have an adverse impact on quality of life.[22] The length of follow up in this study meant that 22% of patients on warfarin consulted their GP with a bleeding event during up to 5 years of follow up.

difference in the time spent in each INR range: patients aged <75 years were within the target INR range 68% of the time, below 2 17%, and over 3 15% of the time. Corresponding values for patients aged ≥75 years were within the target range 68%; below 2 19%, and over 3 13% of the time.

We compared practices using both mean INR and time in range methods. The mean INR for each of the 27 practices supplying INR data was between 2 and 3 (overall mean = 2.46, range = 2.13–2.83). Practice time in range values were calculated as an average of individual patients' time in range; 17 (85%) practices maintained INRs within the therapeutic range for more than 60% of the time.

The INR dataset contained values at the time of, or immediately preceding, 36 of the 86 (41.8%) bleeding complications in the main dataset. In 15 (42%) of these instances, the INR was above 3.

Bleeding events

One hundred and eight patients experienced a total of 141 bleeding episodes. Eighty-six bleeding events occurred on warfarin, 34 on aspirin and 21 with no therapy (seven of these in the small group of patients whose antithrombotic therapy had been withdrawn). Forty-five bleeding episodes were categorised as serious. Table 3 shows the numbers of events categorised by therapy at the time of the complication and age group at 1 April 1998, with rates expressed as events per patient years (expressed as a percentage). A total of 309 patients took warfarin at some stage in the follow up and 67 (22%) of these experienced at least one bleeding event while on treatment. Six (33%) of the 18 patients taking both aspirin and warfarin experienced a bleeding episode during follow up. Annual bleeding risk was higher in patients taking warfarin than in those on aspirin or no antithrombotic therapy (9.0% per year warfarin, 4.7% aspirin and 4.6% no therapy).

There were nine recorded intracranial haemorrhages, two of which occurred after head injury, one in a patient on no treatment and one taking warfarin. One subarachnoid haemorrhage occurred in a patient on aspirin. Four of the six remaining spontaneous intracranial haemorrhages occurred while taking warfarin, two occurred in patients taking aspirin. Ten bleeding episodes were associated with death within 30 days: three gastrointestinal bleeds (two on warfarin, one in an 88-year-old no longer on treatment), two traumatic brain injuries (described above), two spontaneous intracranial haemorrhages (one on aspirin, one on warfarin) and two epistaxes and one urinary bleed which occurred on warfarin.

Patients prescribed no antithrombotic therapy

The study cohort included 102 patients who received neither aspirin nor warfarin. Their mean age at the start of the study was 79.4 years at the start of the study, they had more contraindications to therapy than those given antithrombotic treatment and many were very elderly. In general this group fared badly: three-quarters of those aged ≥75 years on no antithrombotic therapy at the start of the study died and five of the 12 strokes (41.7%) in this group resulted in death within 30 days, compared to seven of 38 (15.7%) in all other groups (P = 0.13).

DISCUSSION

Summary of main findings

GPs provided anticoagulation for up to 51% of an inclusive population sample of predominantly elderly patients with established atrial fibrillation. Adequacy, as judged by measures of INR control, and bleeding rates were comparable with those seen in trials and specialist centres.

Strengths and limitations of the study

Study design and population. Our study addresses an important question concerning the applicability of evidence from controlled trials to routine care. The main strengths were the large community sample, which included many patients who, due to age or comorbidity, would be unable to enter a trial, and the long period of follow up. In particular the study is unusual in monitoring bleeding events in patients with atrial fibrillation not taking warfarin. Nonetheless the study cohort did not represent all patients with atrial fibrillation registered with the practices: it did not include patients who were missed in the searches carried out by practices for the original audit 3 years before the study period, nor did it include patients newly diagnosed since that time. This study is unusual in that almost half of the subjects were in their final 5 years of life.

Data collection and analysis. The method of data collection, using routine primary care records, meant that some hospital-based information that may not have been conveyed in letters to the practice was lost. We did not approach patients directly for medical information in order to avoid sampling bias against those too frail to respond.

We were surprised to find relatively low rates of CT scanning in cases of stroke, possible reflecting the age and rurality of the study population. In many instances the probable stroke was small and occurred in a patient with prior stroke or substantial comorbidity. It is possible that our stroke category may have included some unrecognised intracranial haemorrhages, particularly in patients thought unfit for active management and cannot rule out some of the fatal strokes being due to haemorrhage.

Implications for clinical practice

Two developments are likely to affect the future management of atrial fibrillation in the elderly, one is the BAFTA[23] trial of warfarin against aspirin; the other is the availability of new oral thrombin inhibitors, which appear as effective, but probably no less likely to cause bleeding, than warfarin.[24] For the moment GPs providing anticoagulation services for patients with atrial fibrillation in primary care can be assured that adequate and safe anticoagulation can be achieved in an elderly population.

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Ethics committee

Ethical approval was granted by Dumfries & Galloway Research Ethical Committee, 25 March 2002. Ref 10/11/04

Competing interests

The authors have stated that are none

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REFERENCES

1. Van Walraven C, Hart RG, Singer DE, *et al*. Oral anticoagulants vs. aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002; **288:** 2441–2448.
2. Hart RG, Halperin JL, Pearce LA, *et al*. Lessons from the Stroke Prevention in Atrial Fibrillation trials. *Ann Intern Med* 2003; **138:** 831–838.
3. Sweeney KG, Gray DP, Steele R, Evans P. Use of warfarin in non-rheumatic atrial fibrillation: a commentary from general practice *Br J Gen Pract* 1995; **45:** 153–158.
4. Copland M, Walker ID, Tait RC. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. *Arch Intern Med* 2001; **161:** 2125–2128.
5. Evans A, Kalra L. Are the results of randomized controlled trials on anticoagulation in patients with atrial fibrillation generalizable to clinical practice? *Arch Intern Med* 2001; **161:** 1443–1447.
6. Burton CD, Hamilton KE, Isles CG, Norrie J. Warfarin for nonvalvular atrial fibrillation in primary care — another example of the age paradox? *J Cardiovasc Risk* 2001; **8:** 307–309.
7. Carroll K, Majeed A. Comorbidity associated with atrial fibrillation: a general practice-based study. *Br J Gen Pract* 2001; **51:** 884–891.
8. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ* 2000; **320:** 1236–1239.
9. Dewilde S, Carey IM, Emmas C, *et al*. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation, and predictors of such treatment in UK primary care. *Heart* 2006; **92(8):** 1064–1070.
10. Fitzmaurice DA, Murray ET, Gee KM, Allan TF. Does the Birmingham model of oral anticoagulation management in primary care work outside trial conditions? *Br J Gen Pract* 2001; **51:** 828–829.
11. Torn M, Bollen WL, van der Meer FJ, *et al*. Risks of oral anticoagulant therapy with increasing age. *Arch Intern Med* 2005; **165:** 1527–1532.
12. Goudie BM, Donnan PT, Fairfield G, *et al*. Dependency rather than old age increases the risk of warfarin-related bleeding. *Br J Gen Pract* 2004; **54:** 690–692.
13. Fitzmaurice DA, Kesteven P, Gee KM, *et al*. A systematic review of outcome measures reported for the therapeutic effectiveness of oral anticoagulation. *J Clin Pathol* 2003; **56:** 48–51.
14. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; **69:** 236–239.
15. Wandell PE. Anticoagulant treatment of patients in Swedish primary health care. Safety aspects. *Eur J Clin Pharmacol* 2001; **57**: 61–64.
16. Viitaniemi M, Eskola K, Kurunmaki H, *et al*. Anticoagulant treatment of patients with atrial fibrillation in primary health care. *Scand J Prim Health Care* 1999; **17:** 59–63.
17. Pengo V, Legnani C, Noventa F, *et al*. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A Multicenter Inception Cohort Study. *Thromb Haemost* 2001; **85:** 418–422.
18. Wehinger C, Stollberger C, Langer T, *et al*. Evaluation of risk factors for stroke/embolism and of complications due to anticoagulant therapy in atrial fibrillation. *Stroke* 2001; **32:** 2246–2252.
19. Jackson SL, Peterson GM, Vial JH, *et al*. Outcomes in the management of atrial fibrillation: clinical trial results can apply in practice. *Intern Med J* 2001; **31:** 329–336.
20. Caro JJ, Flegel KM, Orejuela ME, Kelley HE, Speckman JL, Migliaccio-Walle K. Anticoagulant prophylaxis against stroke in atrial fibrillation: effectiveness in actual practice. *CMAJ* 1999; **161:** 493–497.
21. Fahey T, Montgomery AA, Peters TJ. Warfarin therapy for atrial fibrillation: the patient's preference is important [letter]. *Arch Intern Med* 2000; **160:** 2403–2428.
22. Lancaster TR, Singer DE, Sheehan MA, *et al*. The impact of long-term warfarin therapy on quality of life. Evidence from a randomized trial. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *Arch Intern Med* 1991;**151:** 1944–1949.
23. Mant JW, Richards SH, Hobbs FR, *et al*. 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. *BMC Cardiovasc Disord* 2003; **3:** 9.
24. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003; **362:** 1691–1698.