

# The use of antithrombotics in patients presenting with stroke and atrial fibrillation

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**Abstract:** Antithrombotics have been shown to decrease the risk of stroke in patients with atrial fibrillation (AF). However they are associated with an increased risk of bleeding. We assessed the frequency and appropriateness of antithrombotic therapy in patients admitted to our service with stroke and AF. A retrospective case study of 219 patients (mean age 77.2 years) admitted between January 1999 and 31 December 2001 with a diagnosis of stroke and AF was done. Patient characteristics, presence of comorbid conditions, knowledge of preadmission AF, medication history and appropriateness of antithrombotic treatment were recorded. One hundred and fifty patients were known to have had AF prior to admission. Forty-one presented with an intracranial hemorrhage (19 on warfarin, 10 on aspirin). Of those patients with known AF only 43 were on treatment consistent with the guidelines. Warfarin was recommended in 144 of the whole cohort, but only 39 were taking it. Fifty-three patients were receiving aspirin although warfarin was the recommended treatment. Fifty-four with known AF were not on any antithrombotic treatment. Factors significantly associated with the use of antithrombotic treatment were history of AF ( $p = 0.0004$ ), valvular heart disease ( $p = 0.02$ ), venous thromboembolism ( $p = 0.04$ ), risk of thromboembolism ( $p = 0.003$ ) and presentation with a nonischemic infarct ( $p = 0.008$ ). Antithrombotic therapy use in our patients differs significantly from guideline recommendations.

**Keywords:** aspirin, warfarin, atrial fibrillation

## Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke (Atrial Fibrillation Investigators 1994). The risk is increased in patients who have had a previous stroke or transient ischemic attack (TIA), are hypertensive, have congestive cardiac failure, diabetes or are older than 65 years (Laupacis et al 1998; Gage et al 2001). A number of studies have shown that antithrombotic therapy with either warfarin or aspirin is successful in reducing the risk of stroke (Petersen et al 1989; Stroke Prevention in Atrial Fibrillation Investigators 1991; Atrial Fibrillation Investigators 1994; Hart et al 1999; Lip and Boos 2006). Most comparative studies favor warfarin, but major bleeding events are usually more frequent with warfarin (Morocutti et al 1997; Hart and Halperin 1999; Taylor et al 2001). However it should be noted that a recent report from DiMarco and colleagues (2005) has shown similar bleeding risks with either warfarin or aspirin. Warfarin is recommended as first line treatment (unless contraindicated) followed by aspirin in patients with AF who are at high risk of stroke (Laupacis et al 1998; Hart and Halperin 1999). Yet the uptake of warfarin is not as great as one would predict from population studies largely because it is perceived as carrying a high risk of bleeding, requires ongoing monitoring and the elderly (who are most likely to benefit from warfarin) have other risk factors such as increased risk of falls or dementia that place them at risk

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of bleeding complications (Sudlow et al 1998; Bungard et al 2000; Go et al 2003; Laguna et al 2004). Furthermore, in clinical trials anticoagulation is carefully monitored in highly motivated patients, such accuracy might be difficult to achieve in clinical practice.

The subtype of stroke is a further factor to consider when deciding on which agent to employ in at risk patients. Not all ischemic strokes that occur in patients with AF are cardioembolic. It has been estimated that one third of strokes occurring in patients are due to small vessel disease or have an atherosclerotic basis (Evans et al 2000; Hart et al 2000). In these patients antiplatelet therapy may be preferred as there is no difference in mortality or stroke recurrence whether these patients are treated with warfarin or aspirin (Evans et al 2001). In addition it is well known that there is a higher prevalence of AF in older individuals and increasing age is also associated with an increased prevalence of small vessel disease (Atrial Fibrillation Investigators 1994). With an increasing aging population these are necessary factors to consider before commencing therapy. In this study we assessed the frequency and appropriateness of antithrombotic therapy in patients who were admitted to our service with stroke and AF. We decided to include patients who had either ischemic or hemorrhagic strokes as this represents true clinical practice. Unlike the randomized clinical trials, we did not exclude patients in whom warfarin (for example venous thromboembolic disease or valvular heart disease) or aspirin (ischemic heart disease) was clearly indicated.

## Methods

The study was a retrospective case study of patients who were admitted to Capital and Coast District Health Board hospitals with a diagnosis of stroke with documented AF on admission. The sample was recruited by identifying all adult admissions between 1 January 1999 to 31 December 2001 with a primary or secondary diagnosis of any form of an intracranial vascular event using the relevant ICD-10 codes, these being I600–I679 or G450–G468 (International Statistical Classification of Diseases 2000). Each record was examined and patients were included if the admission met the WHO definition for cerebrovascular accident (CVA) or TIA (Hatano 1976). There also had to be ECG evidence of AF. In addition we extracted the following information from the case record: the basic demographic details, presence of co-morbid conditions, history of the presentation including the occurrence of preadmission AF, medication history on admission, initial examination findings, functional assessment using the Barthel score (Tennant et al 1996) within the first

week after admission. Where it was not available the investigators derived a functional grade. This was completed from the patients' functional level as documented in the case notes from physiotherapy, occupational therapy and nursing assessments. Functional grades of low, medium, high and normal were assessed to correspond to a Barthel score of 0–4, 5–9, 10–19 and 20 respectively. Where available transthoracic echocardiographic findings were noted.

## Radiological classification

All CT scans and/or MRI imaging was independently reviewed by an investigator (MN) who was provided with a précis of the relevant clinical features of the presentation. The investigator was blinded to the original radiological report and the antithrombotic treatment status of the patient. The CT scans were classified initially as to whether there was intraparenchymal or extra-axial hemorrhage. Thereafter the lesions were coded according to a modified TOAST classification using a 2 cm cut point (for subcortical and brainstem) instead of 1.5 cm to permit the use of the Miller subtype scheme (Adams Jr et al 1993; Miller et al 1993).

## Subtype of ischemic stroke

The classification of the subtype of ischemic stroke was based on the methodology of Miller and colleagues (1993), but was modified as angiography was only very rarely performed in our hospitals. The patients were classified into one of the following six groups: cardioembolic (definite), cardioembolic (probable), lacunar, atherothrombotic, ischemic (miscellaneous) or ischemic (uncertain). Two investigators (CB and TI) independently placed each stroke into one of the above categories. If there was a difference of opinion, the particular case was discussed and a consensus agreement was reached.

## Questionnaire

A questionnaire was sent to the primary care physician of each patient requesting information on whether the diagnosis of AF was known prior to the admission and if so whether the patient was on treatment for the same. If not a reason for not using either agent was requested. We also requested information on the preadmission functional status of the patient, prior history of a CVA or TIA or both and history of the relevant comorbidity.

## Guideline recommended therapy

Each patient was assigned a guideline recommended therapy of 'warfarin', 'aspirin' or 'either,' according to the

recommendations of Laupacis et al 1998. This is based on categorization of age (<65 years, 65–75 years, >75 years) and the presence or absence of additional risk factors for stroke (TIA, systemic embolus or stroke, hypertension, poor left ventricular function, rheumatic mitral valve disease or prosthetic heart valve). These guidelines, published in 1998, were available prior to the start of the study period and hence represent best practice at the time. These guidelines are very similar to the CHADS<sub>2</sub> Index (Gage et al 2001) that is now more frequently used to assess stroke risk. They differ in the age criterion – >75 years in the CHADS<sub>2</sub> index and an additional point for patients who have had a previous stroke or TIA. As 144 of our patients were 75 years or older it is unlikely that the stroke risks score would have changed significantly.

## Statistical methods

Simple univariate measures of association and t-tests were used to test the association between potential risk factors for the use versus nonuse of any antithrombotic (aspirin or warfarin), and warfarin use versus aspirin or no antithrombotic therapy.

Logistic regression, using a variety of model selection procedures (backwards selection, and stepwise selection), was used to try and establish independent risk factors for antithrombotic use.

Two derived variables were used in the model building process. One was a variable that counted up the number of risk factors for bleeding (a history of prior bleeding, peptic ulcer disease, cognitive impairment, hepatic disease, alcohol abuse and the risk of falling), with possible scores between 0 and 6. The other was a variable that counted up the number of risk factors for stroke in the presence of AF (hypertension, diabetes mellitus, a history of prior stroke or TIA, congestive heart failure and age over 65 years), with possible scores between 0 and 5. The technique appropriate to ordinal variables, the Wilcoxon test, was also used for these derived variables. Log-normally distributed continuous data (INR) are presented as geometric means with geometric confidence intervals and t-tests. SAS version 8.2 (SAS Institute, Cary NC, 2001) was used for the analysis.

The project was approved by the Wellington Regional Ethics Committee.

## Results

During the period of the audit 2090 patients were identified from discharge coding. Of these 219 met the criteria for the study (Figure 1). One hundred and fifty of these were known to have had AF prior to admission.

The characteristics of the patients are shown in Table 1. The mean age of our patients was 77.2 years, 144 of whom were 75 years or older. The risk factors for stroke or bleeding are also shown in Table 1. The mean stroke risk score per individual was 2.19, whereas the mean bleeding risk score was 0.43 per individual.

Forty-one patients were diagnosed with an intracranial hemorrhage, 19 (46.3%) of these were taking warfarin and 10 (24.4%) aspirin on admission. According to recommended guidelines all but one of these patients would have been recommended to have warfarin (Laupacis et al 1998). There were no differences in the INR levels between patients with hemorrhagic strokes or ischemic infarcts (geometric mean INR 1.90 and 2.06 respectively,  $p = 0.57$ ).

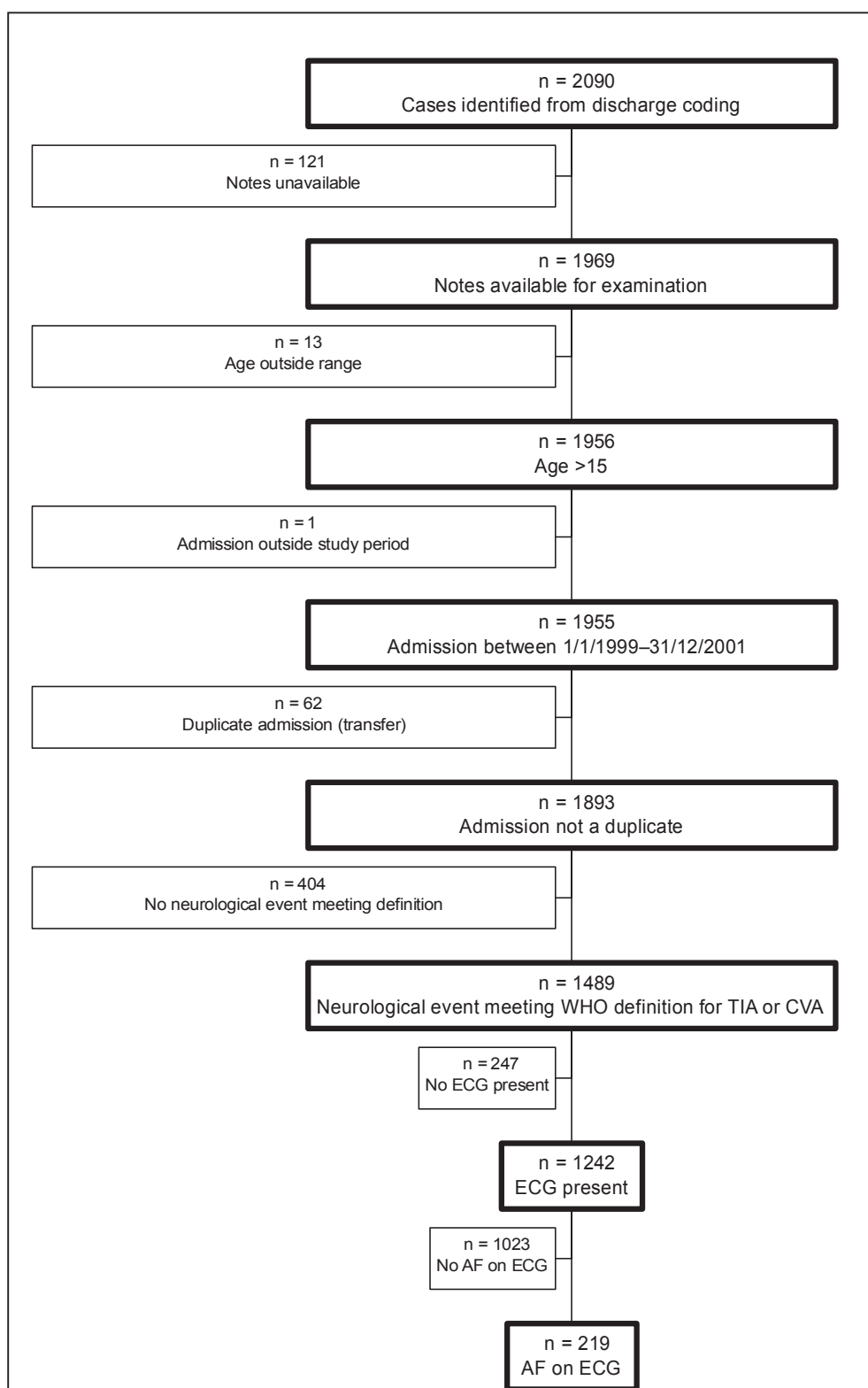
The subtypes of stroke are shown in Table 2. One hundred and forty three of 177 ischemic events (80.8%) were categorized as either definite or probable cardioembolic with the rest being lacunar or ischemic (uncertain). Seventy-one of the 143 patients with a definite or possible cardioembolic stroke were on an antithrombotic agent (warfarin, 17 patients (11.9%) or aspirin, 54 patients (37.8%)). Twelve of the 23 patients with lacunar strokes were on either warfarin (4 patients, 17.4%) or aspirin (8 patients, 34.8%).

Table 3 shows the actual and recommended treatments for the whole cohort and for those whose AF had been diagnosed prior to the present admission.

Of the 150 patients with known AF, only 43 (28.7%) were on treatment consistent with the guidelines. In 144 of the 219 patients warfarin was the recommended agent, yet only 39 patients (27.1%) were taking it. A further 53 patients (36.8%) for whom warfarin was recommended were receiving aspirin. Among all those patients with known AF, 54 patients (36%) were not on any antithrombotic treatment. For the whole cohort a similar percentage (42%) was not taking any antithrombotic treatment.

The factors associated with a greater or lesser likelihood of using antithrombotic treatment are shown in Table 4. In addition patients who had had a previous CVA or TIA or had a history of ischemic heart disease were more likely to be using some form of antithrombotic treatment. Factors that were associated with warfarin use were a history of venous thromboembolism, a history of AF prior to admission, nonischemic (hemorrhagic stroke syndrome) and older age (Table 5).

Sixty-seven patients had an echocardiogram performed. The mean (SD) left ventricular ejection fraction was 56.9 (13.8%); left atrial size 46.6 (10.8 mm) and fractional shortening was 31.2 (8.7)%. Left atrial size was significantly



**Figure 1** Inclusion criteria flow chart.

**Table 1** Patient characteristics

	No. of Patients (%)	
<b>Demographics</b>		
Gender: Male:Female	89:130	(40.6):(59.4)
Age: Mean ( $\pm$ SD)	77.2 years	$\pm$ 11.9
Age: Median (Range)	79.6 years	(31–96 years)
Ethnicity: European	177	(82.7)
Smoker: Current or ex-smoker	80	(36.5)
<b>Risk factors for stroke</b>		
Age >65 years	187	(85.4)
Prior stroke or TIA	91	(41.6)
Congestive heart failure	55	(25.1)
Hypertension	107	(48.9)
Diabetes mellitus	35	(16.0)
Stroke Risk Score (mean $\pm$ SD)	2.19	$\pm$ 1.09
<b>Risk factors for bleeding</b>		
Prior bleeding	12	(5.5)
Peptic ulcer disease	17	(7.8)
Cognitive impairment	33	(15.1)
Hepatic disease	1	(0.5)
Alcohol abuse	7	(3.2)
Documented risk of falling	24	(11.0)
Bleeding Risk Score (mean $\pm$ SD)	0.43	$\pm$ 0.69

larger among those on antithrombotic agents compared with those not on any antithrombotics (49.9 mm versus 43.6 mm respectively,  $p = 0.01$ ). No significant differences were observed between LV ejection fraction ( $p = 0.97$ ) or fractional shortening ( $p = 0.74$ ).

A bleeding history and a history of peptic ulcer disease were associated with a decreased use of any antithrombotic history ( $p = 0.04$ ).

## Discussion

Our study has shown in an unselected group of patients admitted with a stroke syndrome and AF that antithrombotic treatments with either anticoagulants or antiplatelet agents are underused according to contemporary recommendations (Petersen et al 1989; Atrial Fibrillation Investigators 1994;

Stroke Prevention in Atrial Fibrillation (SPAF) Investigators 1991; EAFT Study Group 1993; Laupacis et al 1998; Go et al 2003; Hylek et al 2003; Gage et al 2004; Perez-Gomez et al 2004). Under use was particularly marked with warfarin where only 43 patients (19.6%) were taking the drug prior to admission. According to the guidelines available at the time of the study it would have been indicated in 144 patients. Low uptake has previously been described in the primary care setting where Sudlow and colleagues (1998), noted that only 23% of patients with AF were using anticoagulants. Two more recent studies from the USA (Go et al 2003; Wang et al 2003) showed differing uptake of anticoagulation after AF was diagnosed. Go and colleagues (2003) noted that nearly 55% of their cohort with nonvalvular AF and in whom there was no contraindication to warfarin were prescribed this drug whereas Wang et al 2003 noted in a community based survey that 705 of 861 patients with AF were not treated with warfarin, however it is not clear from this study how many of the patients had contraindications to anticoagulation. Wang and colleagues (2003) point out that using their risk score, stroke rates in patients with low scores (45% of their cohort) were of the order of 1.1 to 1.5 strokes per 100 person years which would suggest that this may be near the threshold for the use of anticoagulants. Our patients seem to have had more severe disease than those of Wang and colleagues (2003) as most of them had co-morbidities that would have placed them in a moderate to high-risk stroke group.

Overall, the uptake of warfarin in patients with nonvalvular AF has remained a problem despite adequate publicity of its effectiveness with quoted prescription rates of 15%–44% (Bungard et al 2000; Iqbal et al 2005). The reasons provided for not using warfarin by the primary care physicians in our study were similar to those enunciated by Bungard and colleagues (2000), in that they included past history of bleeding, noncompliance, cognitive difficulties, frailty and patient choice. Although not mentioned by our practitioners we think that lack of a monitoring centre for anticoagulation probably also played a role in the nonprescription of this drug. Use of warfarin is time consuming for a general practitioner and we think this may have proved a barrier for our prescribers.

Even where anticoagulants are prescribed there might be significant drop out rate. Evans and colleagues (2000), noted in a sample of 288 patients that 74 stopped taking warfarin, 25 because of bleeding complications and 37 for reasons such as choice, compliance or logistics. Similar findings were reported from the much larger AFFIRM Study where 33.6% of the trial participants discontinued warfarin use for some period during the trial. The major reason for withdrawal was maintenance of

**Table 2** Stroke details

Variable	No. of Patients (%)	
Characteristics of stroke		
Ischemic stroke	177	(80.8)
Nonischemic	41	(18.7)
Nonvascular	1	(0.5)
Ischemic stroke subtype (% of Ischemic)		
Cardioembolic-definite	104	(58.8)
Cardioembolic-probable	39	(22.0)
Lacunar	23	(13.0)
Atherothrombotic	0	(0.0)
Ischemic uncertain	11	(6.2)



**Table 3** Antithrombotic treatment versus guideline recommended therapy

Actual treatment	Guideline recommendations <sup>a</sup>				Total
	Warfarin	Warfarin OR Aspirin	Aspirin	Neither	
All subjects (n = 219)					
All Subjects					
Warfarin AND Aspirin	3	0	0	0	3
Warfarin	39	1	0	0	40
Aspirin	71	3	1	0	75
Neither	91	4	6	0	101
Total	204	8	7	0	219
Subjects with known atrial fibrillation (n = 150)					
Subjects with known AF					
Warfarin AND Aspirin	2	0	0	0	2
Warfarin	37	1	0	0	38
Aspirin	53	2	1	0	56
Neither	52	0	2	0	54
Total	144	3	3	0	150

<sup>a</sup>Notes: Based on the guidelines presented by Laupacis et al 1998.

sinus rhythm, but bleeding was the second most common reason for stopping warfarin (DiMarco et al 2005).

Efforts suggested to improve the use and compliance with warfarin have included home follow-up following initiation of warfarin in hospital. Jackson and colleagues (2004) compared usual care (namely, managed totally by the general practitioner) with a project pharmacist who visited patients at home and adjusted the dose of warfarin accordingly. Using this programme the pharmacist arm of the study achieved a significantly greater proportion of patients with a therapeutic INR early in treatment with less bleeding events as well. A pharmacist led programme is attractive because they are familiar with drug interactions and the difficulties with using warfarin. They are also likely to maintain the INR in the therapeutic range. This will decrease the risk of bleeding and also decrease the risk of stroke as patients

who are under anticoagulated have a similar risk of stroke as those who are treated with placebo. Funding for such an arrangement might prove difficult in New Zealand where it would have to come from the local District Health Board. If this were not forthcoming it would be difficult to see where the salaries for the pharmacists would be found.

Other options to make warfarin use more attractive relate to self-monitoring of the INR in a similar fashion as diabetics monitor blood glucose. Two recent studies have shown markedly different outcomes. Gardiner and colleagues (2004) showed that self-testing in 84 patients from an anticoagulation clinic was effective and acceptable. However the trial was open and not controlled. It involved 84 patients who were self selected from 800 who were invited to take part. The average age of the trialists was less than the average age of other patients in the anticoagulation clinic. The second study reported by Murray and colleagues (2004) was a randomized controlled trial involving 608 (of 2586 invited) patients. Three hundred and twenty seven patients were randomized to self-management, but of these 26% were unable to complete training. Factors that were associated with success in training and continuing in the trial were younger age and more education. The authors point out that 76% of the original cohort chose not to undertake self testing and their recommendations were that standardization and dissemination of training would be needed with adequate backup from clinicians if this method was to be successful. In summary some form of central control of anticoagulation seems to be the best method to increase the use of warfarin.

Our study also demonstrated potential problems with the use of antithrombotics. Forty-one of our 219 patients (18.7%) presented with hemorrhage. Nineteen of these

**Table 4** Factors associated with the use or nonuse of antithrombotic drugs<sup>a</sup>

Variable	Odds ratios (95% CI) <sup>b</sup>		p value
History of AF	3.4	(1.74–6.65)	<b>0.0004</b>
History of valvular heart disease	15.1	(1.62–141.1)	<b>0.02</b>
History of venous thrombo-embolism	4.2	(1.07–16.4)	<b>0.04</b>
Risk of bleeding score <sup>c</sup>	0.68	(0.44–1.05)	0.08
Risk of thrombo-embolism score <sup>c</sup>	1.58	(1.16–2.13)	<b>0.003</b>
Ischemic infarct <sup>d</sup>	0.32	(0.14–0.74)	<b>0.008</b>

<sup>a</sup>Notes: <sup>a</sup>Multivariate model; <sup>b</sup>Odds ratio >1, more likely to be using any antithrombotic; <sup>c</sup>per increase in one risk factor; <sup>d</sup>During index admission.

**Table 5** Factors associated with the use or nonuse of warfarin<sup>a</sup>

Variable	Odds ratios (95% CI) <sup>b</sup>		P value
History of AF	16.7	(4.0–69.7)	<b>0.0001</b>
History of venous thrombo-embolism	14.1	(3.6–54.7)	<b>0.0001</b>
Age <sup>c</sup>	0.96	(0.93–0.99)	0.083
Ischemic infarct <sup>d</sup>	0.13	(0.05–0.32)	<b>&lt;0.0001</b>

**Note:** <sup>a</sup>Multivariate model. Warfarin versus aspirin alone or no-antithrombotic;

<sup>b</sup>Odds ratio >1, more likely to be using any antithrombotic; <sup>c</sup>per year older; <sup>d</sup>During index admission.

were extra-axial (9 patients were taking warfarin, 4 aspirin and 6 neither), the rest were intracerebral (10 patients on warfarin, 5 on aspirin and 6 neither). Although one cannot be sure that the drugs were responsible for the hemorrhage they do seem to be over represented. These findings are of importance and confirm the results of others who have noted that warfarin is associated with a significantly increased risk of bleeding when compared to aspirin or placebo (Taylor et al 2001; Go et al 2003; DiMarco et al 2005). This risk needs to be balanced against the risk of stroke in patients with nonvalvular AF.

Although the potential benefits of warfarin therapy in high-risk populations have been clearly demonstrated (Lip and Boos 2006) the decision to prescribe any agent has to be balanced against the risk (or “perceived risks”) from therapy. These risks are often difficult to quantify in the individual patient and older patients who are likely to gain most benefit are often considered to be at higher risk. Our data suggests that often where warfarin therapy was recommended aspirin was substituted. Aspirin is significantly easier to prescribe as it does not require blood test monitoring, is used in a fixed dose and is considered safer than warfarin in regard to bleeding complications, despite bleeding risks with either treatment being small (Koudstaal 2000). Furthermore, a significant percentage (28.3%) of our patients may have been on aspirin for ischemic heart disease (IHD), in such patients aspirin would be indicated and our prescribers may not have wished to add warfarin to aspirin for fear of an increased bleeding risk. Yet, as mentioned earlier warfarin is superior to aspirin in preventing stroke in patients with AF.

Investigators have assessed a combination of warfarin and aspirin using a subtherapeutic INR of 1.5–1.9. Such trials have not proved successful in preventing stroke in patients with AF (SPAF III Investigators 1996; Gullov et al 1998; Edvardson et al 2003). A more recent study compared a combination of triflusal (a cyclooxygenase inhibitor) and therapeutic warfarin against therapeutic warfarin in high-risk patients with AF and in a second group compared triflusal alone

versus a combination of triflusal and warfarin (INR titrated to 1.25 to 2) in patients with an intermediate risk of stroke (Perez-Gomez et al 2004). The results showed added benefit in stroke prevention with the combinations with no increase in bleeding risk, but the patients were very closely monitored and the median INR in the intermediate group was 1.93 and 2.17 in the high-risk group respectively. The result particularly with the intermediate risk group would suggest that the INR should be at a level near to 2 to gain any benefit. Therefore this might be an option when using warfarin particularly in intermediate risk patients. We had a small number of patients with lacunar infarcts, this may represent the assessment system that we used, but the placement in this group depended on the clinical picture and the CT scan report. Approximately 50% of these patients were on some form of antithrombotic treatment. Of the 12 patients, 8 were taking aspirin and 4 warfarin. Aspirin may be the preferred agent in these patients as it is equally effective and is safer than warfarin (Evans et al 2001). Although aspirin is recommended in patients with either contraindications to warfarin or small vessel disease it should be noted that for many of our patients this was the first presentation of cerebrovascular disease and thus without prior imaging it would potentially be difficult to know which patients would be suitable for aspirin.

In conclusion, we have shown that in patients presenting to hospital with stroke syndromes and atrial fibrillation, anti-thrombotic treatment is underused and differs significantly from guidelines. We have suggested changes to correct practice that should make warfarin more frequently used. We believe an anticoagulation service with significant pharmacist input would offer the best solution.

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