Anticoagulants in atrial fibrillation

Numerous studies have investigated the relative efficacies of warfarin and aspirin compared with placebo for prevention of stroke in patients with atrial fibrillation, and the evidence overwhelming shows that warfarin is more effective. Until recently, the use of warfarin in patients aged 75 years or older was controversial because of safety concerns, but the BAFTA study demonstrated that warfarin is as safe as aspirin in this age group. Therefore, all patients with atrial fibrillation should be considered for warfarin therapy—apart from those patients younger than 65 years who have no additional risk factors.

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Atrial fibrillation is a disease of the elderly population and it is becoming increasingly common.[1] The increase in prevalence is partly due to the ageing population, and partly due to better treatment of coronary heart disease—especially as more people now survive a myocardial infarction. During the last decade or so, that atrial fibrillation is not a benign condition has become increasingly clear. It is associated with excess mortality (from coronary disease) and an increased risk of stroke.

Several large trials have demonstrated the effectiveness of oral anticoagulation for reducing these outcomes, with particularly strong data supporting the use of oral anticoagulation for both primary and secondary prevention of stroke. This article outlines the evidence for oral anticoagulation in the long-term treatment of atrial fibrillation.

Why is atrial fibrillation important?

The Framingham study was the first to show that atrial fibrillation is an independent risk factor for stroke, even in the absence of mitral valve disease (non-rheumatic atrial fibrillation).[1] Both the Whitehall study[2] and the British Heart study[3] confirmed that non-rheumatic atrial fibrillation increased the risk of stroke. But these studies demonstrated different relative risks to each other and to that seen in the Framingham study. The underlying risk of stroke in the control populations was also different (table 1).[4] Therefore, the risk of stroke in patients with non-rheumatic atrial fibrillation is the primary consideration in management, particularly considering that oral anticoagulation has its own risks (ie, bleeding).

A multivariate analysis[5] revealed several significant additional risk factors for the prediction of stroke in patients with non-rheumatic atrial fibrillation. First, the annual risk of stroke in control patients younger than 65 years, with no other risk factors

	Risk of stroke with no atrial fibrillation or rheumatic disease	Risk of stroke with non-rheumatic atrial fibrillation (95% CI)	Excess stroke attributable to non-rheumatic atrial fibrillation (range)	Relative Risk (95% CI)
Framingham[1]	2·9	42 (25–64)	39 (23–61)	5·6 (3·4–8·4)
Whitehall[2]	0·9	14 (5–23)	13 (4–23)	6·9 (3–13·5)
British Heart[3]	1·6	3 (0·1–22)	2 (0–21)	2·3 (0·1–12·7)

Table 1: Relative risks of stroke associated with non-rheumatic atrial fibrillation
*Rate of stroke per 1000 person years

was 1%. This increased to 8·1% for patients older than 75 years, with one or more additional risk factors. Warfarin reduced the risk of stroke in all subgroups except for those younger than 60 years who had no other risk factors, and in whom the incidence of stroke was less than 1%.

Factors that did increase risk of stroke were: history of hypertension (relative risk 1·6 [95% CI 1·3–2·8]); history of diabetes (1·7 [1·2–3·6]); history of prior stroke or transient ischaemic attack (2·5 [1·2–5·3]); history of myocardial infarction (1·7 [1·1–2·7]); and history of congestive heart failure; (1·7 [1·1–2·5]).

Lip[6] found that paroxysmal (self-limiting) atrial fibrillation did not confer an increased risk of stroke, but he was not able to calculate the number of patients who converted from paroxysmal to persistent fibrillation. The risk of thrombosis associated with paroxysmal atrial fibrillation probably relates to the frequency and duration of paroxysms and the presence of associated risk factors, such as structural heart disease or hypertension.[6]

In clinical practice, assuming that the risk of stroke is constant between paroxysmal and persistent atrial fibrillation is the safest option. Individual studies have suggested that the presence of angina is a risk factor, but the significance of this factor was lost within multivariate analyses and may be a coincidental finding due to the increasing prevalence of angina with age.[5]

Effective oral anticoagulants potentially have a role in the prevention of systemic embolism, particularly to the brain. To determine the role of warfarin as a thromboprophylactic agent for patients with non-rheumatic atrial fibrillation, the following questions needed to be answered:

- What is the incidence and prevalence within the general population?
- Which patients would benefit from some form of prophylaxis against embolic stroke?
- What are the risk and benefits associated with antiplatelet therapy as opposed to oral anticoagulation therapy?
- What are the optimum intensities of therapy for warfarin treatment?

How common is atrial fibrillation?

Various studies have investigated the incidence and prevalence of atrial fibrillation, but attempts to quantify existing data have been confounded by differences in diagnostic criteria and quantification of associated medical conditions. A meta-analysis of large community studies, however, revealed some consistency in findings between investigations from different countries.

The prevalence of atrial fibrillation increases with age: from 2·3% in those aged 40 or older, to 6% in those aged 60 or older, and 10% in those older than 80 years.[7,8] Overall in the UK, the community prevalence is estimated to be 0·89%.[7] Although prevalence is higher in men at all ages, because women live longer, the total number of patients with atrial fibrillation is about equal between the sexes. Furthermore, approximately 50% of patients with this condition are aged 75 years or older, and more than half of them are women.

The SAFE study[9] investigated screening strategies in 50 primary-care centres to identify patients with atrial fibrillation. In half of the centres (intervention practices), patients were randomly allocated to systematic screening (invitation for electrocardiography) or to opportunistic screening (taking the pulse and invitating for electrocardiography if pulse was irregular). No active screening took place in the other centres (control practices).

Nearly 15,000 patients were screened at intervention practices over 12 months. The detection rate of new cases of atrial fibrillation in these practices was 1·63% a year compared with 1·04% in control practices (difference 0·59%, 95% I 0·20–0·98%). Systematic and opportunistic screening detected similar numbers of new cases (1·62% versus 1·64%; difference 0·02%, −0·5–0·5%). This study also demonstrated a prevalence of 7·2% in a population aged 65 years or older, with a 10·3% prevalence in those aged over 75 years. These findings represent the most robust incidence and prevalence data from the UK.

Benefits and risks of warfarin versus placebo

Several randomised, controlled studies have investigated the role of anticoagulation for stroke prevention in non-rheumatic atrial fibrillation. Eight randomised studies, published before 2000, provided data for the selection of patients for anticoagulation, the relative merits of antiplatelets versus anticoagulation, and the risk stratification for patients with atrial fibrillation with and without other risk factors for stroke.[10–17] The relative risk reduction of warfarin compared with placebo is shown in table 2.

All these studies were based in secondary care, and so we need to be cautious about extrapolating

their data to patients in primary care—particularly given the highly selected populations chosen for investigation in these studies.[18] Despite 97% of potential participants being excluded before randomisation, a large percentage of patients withdrew in all these trials.[11] The highest rate of withdrawal occurred in the study that used a population most similar to that found in primary care.[10]

Interpretation of the results of these studies is also problematic: different levels of anticoagulant intensity were employed and actual levels of intensity achieved were either not stated or not subject to direct comparison (using prothrombin ratio rather than international normalised ratio [INR]).

If we consider that the risk of haemorrhagic side-effects is increased on initiation of therapy and that with thrombotic side-effects are artefactually low due to survival bias, then we have other methodological problems. Therefore, patients with non-rheumatic atrial fibrillation who had already undergone a thrombotic episode, such as stroke, would be excluded from these studies.

The Atrial Fibrillation Investigators did a meta-analysis[19] of five primary-prevention studies they had authored.[10–13,15] Notwithstanding concerns regarding the selection of patients for these studies, different risk factors clearly influence the therapeutic decision. The five studies covered 1889 patient-years for those receiving warfarin and 1802 patient-years for the control group. For the aspirin-to-placebo comparisons, 1132 patient-years of aspirin and 1133 of placebo were measured.

The primary endpoints were ischaemic stroke and major haemorrhage, as assessed by each study. Patients within the control groups who had no history of transient ischaemic attack or stroke, hypertension or congestive heart failure, diabetes, angina, or myocardial infarction had an annual incidence of stroke of 1·5%.

Warfarin was consistently effective for the prevention of ischaemic stroke with a 68% reduction in the incidence of all strokes (95% CI, 50–79%), representing an absolute annual reduction of 3·1% (p<0·001). This risk reduction must be viewed in the light of a reported low incidence of side-effects, particularly haemorrhagic stroke, which may represent selection bias.

The absolute reduction in risk, however, may have been underestimated because the analysis was performed on an intention-to-treat basis, when in fact 8 of the 27 patients in the warfarin group who had a stroke were not receiving warfarin at the time. Warfarin decreased the death rate by 33% (95% CI 9–51%; p=0·10) and the rate of the combined outcome of stroke, systemic embolism, or death by 48% (95% CI 34–60%; p<0·001).

The studies clearly indicate that some patients with atrial fibrillation would benefit from oral anticoagulation, some would benefit from antiplatelet therapy, and others would be best served by giving no treatment.

	Annual event rate		Relative risk reduction of warfarin
	Placebo	Warfarin	
AFASAK[10]	4·8%	1·4%	71%
BATAAF[12]	2·9%	0·4%	86%
SPAF I[11]	7·4%	2·3%	67%
CAFA[13]	3·7%	2·1%	43%
VETS[15]	4·3%	0·9%	79%
EAFT[14]	17%	8·0%	53%

Table 2: Relative-risk reduction seen in studies of thromboembolism from warfarin compared with placebo

Warfarin or aspirin?

Four studies randomised patients to receive aspirin.[10,11,14,16] The Danish AFASAK trial,[10] with a 75 mg daily dose, showed a non-significant reduction in rate of stroke compared with placebo. But, the SPAF study,[11] noted a reduction of 44% (95% CI 7–66%) in the incidence of stroke at a daily dose of 325 mg. A meta-analysis of these studies[16] confirmed that oral anticoagulation is twice as effective as aspirin for prevention of ischaemic stroke in patients with atrial fibrillation. Furthermore, the beneficial effects of aspirin do not appear to be dose-related.[20]

The EAFT study[14] was a secondary prevention study of 300 mg aspirin daily compared with warfarin or placebo. No significant reduction in thromboembolic disease was observed in the aspirin-treated group when compared with placebo, with warfarin

achieving a statistically significant improvement (when compared with placebo). Treatment with aspirin or other platelet inhibitors may have benefits in terms of safety, cost, and convenience (no need for regular blood tests), but current evidence suggests that aspirin is less effective for prevention of stroke than is warfarin.

The SPAF-II study showed that adding aspirin to warfarin is not an effective strategy.[17] 1044 patients with atrial fibrillation and at least one other risk factor for thromboembolic disease were randomised to receive either warfarin to a target INR of 2–3 or a fixed-dose of warfarin to INR 1·2–1·5 plus 325 mg aspirin. The study was stopped after a mean follow-up of 1·1 years because of increased incidence of primary events (ischaemic stroke and systemic embolism) for patients on combination therapy ($p<0·0001$). Additionally, a cost-effectiveness analysis using data from the USA supports the view that warfarin is preferred to aspirin or to no treatment in terms of quality-adjusted-life years for all patients with non-rheumatic atrial fibrillation.[21]

Aspirin appears to minimally increase the risk of haemorrhagic stroke. A meta-analysis[22] of randomised controlled trials using aspirin found that at a mean dose of 273 mg per day, the absolute risk of haemorrhagic stroke increased by 12 events per 10,000 people. This increase in risk is very small, and must be weighed against the reductions in risk of myocardial infarction (137 events per 10,000 with aspirin) and ischaemic stroke (39 events per 10,000 with aspirin).

For patients with atrial fibrillation younger than 65 years with no other risk factors, the benefit of warfarin is minimal compared with no therapy because of the low underlying risk of stroke in these patients. Treatment decisions should ultimately depend on the patients' perception of the inconvenience and harm associated with taking warfarin.[21] Thus, although alternatives to warfarin may be preferred in terms of safety profile, evidence for their routine use is not yet available.

Therefore, for the reasons mentioned, treatment decisions need to be based on an individual's risk assessment. The NICE guidance for the management of atrial fibrillation includes a formal algorithm that is problematic. Using this algorithm, most patients would be assessed as at moderate risk, and should be given either oral anticoagulation or aspirin.[23] A more widely used assessment tool is the CHADS2 system, which gives one point each for congestive heart failure, hypertension, age greater than 75 years, and two points for a history of stroke or transient ischaemic attack. The risk of stroke increases with total score.[24]

Until recently, patients older than 75 years were the most controversial age group with regard to oral anticoagulation.[7] The concern was that the benefits of warfarin did not outweigh the risk of bleeding, which led to uncertainty as to whether or not aspirin would be a safer option in this population. However, patients who took aspirin would be at greater risk of stroke; supported by a meta-analysis of post-hoc analyses of patients older than 75 years from trials of warfarin versus aspirin.[25] The BAFTA study[26] directly answered this uncertainty, showing that warfarin was 65% more effective than aspirin but of equal safety in terms of bleeding risk in high-risk elderly people. These data have now been used to update the van Walraven meta-

analysis, confirming the therapeutic benefit with comparable safety of warfarin in the over 75s (in press).[27]

The therapeutic range for oral anticoagulation

The target level of anticoagulation (INR) in studies ranged between 1·2–1·5 and 2·8–4·2. Data show that the risk of stroke for patients with atrial fibrillation rises steeply below an INR of 2,[28] but the risk of haemorrhage increases rapidly with INR greater than 4.[29] Interpretation of these data is consistent with regard to the recommended lower level, with INR of 2 being almost universally accepted.[30] The upper limit of INR is more widely debated, ranging between 3 and 4. The aim may be to keep INR below 4, but this is unlikely to be successful unless the target INR is set at 3, given the weaknesses associated with current models. The target for INR should therefore be 2·5.

Summary of recommendations

As the evidence exists at present, all patients with atrial fibrillation should be considered for oral anticoagulation (with a target INR of 2·5), apart from those patients under 65 years of age with no additional risk factors. Patients who cannot tolerate oral anticoagulation should be considered for aspirin.

I have no conflict of interest.

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