Warfarin and aspirin as thromboprophylaxis in atrial fibrillation

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- 1 Anticoagulant therapy with warfarin is now established as effective thromboprophylaxis against stroke in atrial fibrillation, in high-risk persons. Aspirin is indicated in moderate-risk persons or if warfarin is contraindicated.
- 2 Risk stratification is suggested, using clinical factors supplemented by echocardiography, to aid choice of prophylaxis.
- 3 Further studies are required to establish how best to identify undiagnosed patients who have atrial fibrillation; to develop new therapeutic strategies; and to refine risk stratification to define which patients with atrial fibrillation are at the highest risk of stroke.

Keywords atrial fibrillation warfarin aspirin stroke thromboembolism

Introduction

Atrial fibrillation is the commonest cardiac arrhythmia in the community, with a prevalence of 2 to 5% in the general population over the age of 60 years. As this arrhythmia is associated with increased mortality and increased risk of thromboembolism, especially stroke, there are important therapeutic considerations, as regards the need for antiarrhythmic and antithrombotic therapy.

However, it is only in the last few years that the efficacy of antithrombotic therapy in preventing strokes in atrial fibrillation has been established by prospective clinical trials. The purpose of this review is to discuss the current status of antithrombotic prophylaxis in atrial fibrillation, its place in the treatment of such patients, and possible management strategies.

in those aged over 75 years [3]. In the United Kingdom, there have been few studies of the prevalence of atrial fibrillation in the community [4–8], and these have been criticised for being too small and unrepresentative [9]. For example, Hill *et al.* [4] screened 819 general practice patients, and found 30 subjects (3.7%) in atrial fibrillation. Kennedy & Caird [7] studied the electrocardiograms of 400 elderly people over 65 years, and found that only 11 patients had atrial fibrillation. In a recent audit of a general practice list of about 10000 patients, we found 67 patients who were currently in atrial fibrillation, or who are known to have past episodes of the arrhythmia; this prevalence increased with age, rising from 1.5% in the sixth decade to 8% in the ninth [10]. Sudlow *et al.* [9] estimated that atrial fibrillation may in fact be more prevalent in this country compared with data from the United States or Australia, and suggests that 'between 160 000 and 644 000 patients aged over 65 years in Great Britain would have atrial fibrillation'.

Atrial fibrillation: epidemiology and pathophysiology

Prevalence of arterial fibrillation

Estimates of the prevalence of atrial fibrillation vary widely around the world. In the Framingham study, for example, the prevalence of atrial fibrillation increased with age (from 0.5% at age 50–59 years to 8.8% at 80–89 years) [1, 2]. A study from the Brusselton community in Western Australia reported a prevalence that increased from 1.7% at age 60–64 years to 11.6%

Atrial fibrillation mortality and stroke

Atrial fibrillation is usually present in about 15–20% of patients with acute stroke, and is associated with a 1.5 to 3.0 fold higher mortality than that for stroke patients who are in sinus rhythm [11, 12] (Table 1).

Non-rheumatic atrial fibrillation has generally been associated with a fivefold increase in the risk of ischaemic stroke compared with that of sinus rhythm, and with a 5–7% yearly risk, which increases with age [13].

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Many studies have confirmed that the presence of atrial fibrillation is an important risk factor for stroke and other thromboembolic events [2, 14, 15]. In the Framingham study, for example, the annual rate of stroke for patients in atrial fibrillation was approximately 4% [16], which was comparable with those in two other studies: the Copenhagen AFASAK study and the Stroke Prevention in Atrial Fibrillation Study, where the annual incidence of stroke among placebo patients was 4.9% [17, 18]. In several large epidemiological studies (Table 1), the stroke rate varied between 0.3% and 4.5% per year.

There is a clear relationship between stroke rate and age in patients with atrial fibrillation. In the pooled analysis of the atrial fibrillation trials, for example, the annual stroke rate in patients with atrial fibrillation, but without coexistent cardiac disease, was 1.6% in those aged 60–69 years old, 2.1% in those aged 70–79 years, and 3.0% in those over age 80 years [19]. In elderly patients (mean age 79.3 years), the presence of nonvalvular atrial fibrillation was an important factor in fatal massive cerebral infarction [20]. Computed tomography studies have also shown that silent ischaemic cerebral infarction is present in 26% of patients with non-rheumatic atrial fibrillation [21].

Pathophysiology

The basic pathophysiological mechanism for thrombus formation and embolism appears to be abnormalities in

blood flow within the fibrillating (and possibly dilated) left atrium. This predisposes to thrombus formation and arterial embolism, especially in the presence of underlying heart disease. The presence of the latter, including valvular heart disease, hypertensive heart disease, a dilated left atrium and poor left ventricular function, is a significant risk factor for stroke and thromboembolism in atrial fibrillation [20, 22]. For example, the thromboembolic risk of atrial fibrillation is 18 times greater if rheumatic heart disease is present [23]. The presence of recent (within 3 months) congestive heart failure and left ventricular dysfunction also contribute to an increased risk of stroke in atrial fibrillation [24, 25]. The importance of cardiac impairment in thromboembolic risk has long been recognized, as thromboembolism is a frequent cause of death in patients with congestive heart failure, occurring in nearly a third of patients, which is partly reduced by prophylactic anticoagulation [26]. Despite this, anticoagulant prophylaxis has not been widely used in patients with left ventricular dysfunction.

An increased left atrial size in patients with atrial fibrillation contributes to an increased risk of intra-atrial thrombi formation and thromboembolism. Although previous evidence had suggested that left atrial enlargement was the cause rather than a consequence of atrial fibrillation [27], recent studies have suggested the converse, that left atrial enlargement may be consequent upon the duration of atrial fibrillation [28–30]. This is relevant as the risk of thromboembolism increases with the duration of atrial fibrillation [22, 31,

Table 1 Stroke rates and mortality in atrial fibrillation. Examples of studies in the literature

Study and country of origin	Reference	Stroke rate	Mortality	Comment
		AF vs no AF (%/year); Relative Risk (RR)	AF vs no AF (%/year); Relative Risk (RR)	
British Regional Heart, United Kingdom	76	0.3; RR 2.3	—	General practice sample
Busselton, Australia	3	—	RR 1.92	Prospective study in elderly population; 2–17 year followup
Edinburgh, Scotland	77	—	67.0 vs 27.3; RR 2.3	Prospective study of elderly population; 5 years followup
Framingham, United	1, 78, 79	(non-rheumatic) 4.1 vs 0.29 RR 5.6 (rheumatic) 4.5 vs 0.29 RR 17.6	(All cause) males: 59.2 vs 34.3; RR 1.7 females: 44.9 vs 25.3; RR 1.8	Population sample, 24 year followup
Manitoba Followup Study, Canada	80	RR 2.07	RR 1.31	Prospective study amongst male air crew recruits; 44 year followup
Reykjavik, Iceland	81	4.4; RR 7.1	32.0 vs 20.0; RR 1.9	Population sample, 14 year followup
Shibata, Japan	82	RR 5.56	—	Prospective population study of stroke, 6.5 year followup
Whitehall, England	83	1.8; RR 6.9	RR 2.6	Male civil servants screened; 18 year followup

32]. A left atrial size of ≥ 4.0 cm has also been previously identified as the single strongest predictor of increased risk for embolization [22]. For example, patients with lone atrial fibrillation (that is, those who have no underlying cause for their arrhythmia), have been shown to have a low risk of stroke and usually have an atrial size < 4.0 cm [33]. Left atrial enlargement has also been associated with the presence of 'spontaneous echo contrast' on transoesophageal echocardiography. This refers to the presence of a smoke-like appearance of blood within the enlarged atrial cavity, suggesting stasis of intra-atrial blood flow, which causes erythrocyte and platelet aggregation, and thrombus formation [32]. The rheological mechanism for spontaneous echo contrast is thought to involve plasma fibrinogen and aggregates of platelets and erythrocytes [34, 35]. By contrast, the absence of spontaneous echo contrast has been associated with a low thromboembolic risk. Early cardioversion has been performed in such patients without oral anticoagulant therapy, with no excess in embolic events [36].

Hypertension and diabetes are risk factors for stroke and the presence of these conditions also increases (by nearly two-fold) the risk of stroke and thromboembolism in atrial fibrillation [19]. The presence of left ventricular hypertrophy secondary to hypertension is another important risk factor for stroke, and atrial fibrillation may add to this risk.

A previous history of stroke, transient ischaemic attack or other thromboembolic episodes substantially adds to the risk of stroke in atrial fibrillation (relative risk 2.5) [19, 24]. In addition, patients admitted with acute stroke who had atrial fibrillation (25%) had a significantly higher in-hospital mortality than stroke patients in sinus rhythm (67% *vs* 44%) [11]. This finding was confirmed in the Oxfordshire community stroke project, where the 17% of patients with acute stroke and atrial fibrillation had a higher 30 day mortality than that in patients in sinus rhythm (23% *vs* 8%) [12]. In the latter study, however, those with stroke and atrial fibrillation who survived at least 30 days had a subsequent risk of recurrent stroke or cardiovascular death which was similar to those in sinus rhythm [12].

The duration and onset of atrial fibrillation may also be of importance. The onset of atrial fibrillation may be temporally related to the occurrence of stroke. In the Framingham study, for example, atrial fibrillation was present at the time of stroke onset in 24% and about a third of the strokes associated with atrial fibrillation occurred within 6 months of onset of the arrhythmia [37]. In addition, stroke recurrence in the first 6 months following the initial event was more common in patients with chronic atrial fibrillation (47% compared with 20% in non-atrial fibrillation group) [37]. However, this finding was not confirmed in the Oxfordshire study [12].

Paroxysmal atrial fibrillation has usually been associated with an intermediate risk of stroke when compared with patients with chronic atrial fibrillation and patients with sinus rhythm. This condition is important as many patients with paroxysmal atrial fibrillation progress to

develop chronic atrial fibrillation, and thromboembolic complications frequently occur soon after the transition from paroxysmal atrial fibrillation to chronic atrial fibrillation [38, 39]. The recent Atrial Fibrillation Investigators pooled analysis suggested a similar stroke risk in persons with paroxysmal atrial fibrillation and chronic atrial fibrillation [19].

Clinical trials of warfarin and aspirin prophylaxis in atrial fibrillation

Until recently, the only evidence supporting the benefit of anticoagulation therapy in prophylaxis has been from retrospective studies. One example is the Montreal Heart Institute Study, which found that the incidence of thromboembolic events was eight times more frequent during the period without anticoagulation therapy, whether or not mitral valve disease was present and regardless of whether or not atrial fibrillation was chronic or paroxysmal [40].

In the mid-1980s, five randomised prospective clinical trials were independently initiated to study the value of antithrombotic prophylaxis in atrial fibrillation [17, 18, 41–43]. All five primary prevention studies (most patients enrolled had no history of embolism) show consistent results (Table 2). Commendably, the investigators who conducted these primary prevention trials agreed to combine their data in a prospective pooled analysis [19]. Also, since these five studies were published, one further primary prevention trial has been published [44], and one secondary prevention trial in patients with non-rheumatic atrial fibrillation and a history of transient ischaemic attack or minor stroke [45]. Despite the limitations (which will be discussed further below), consideration of all seven trials together, as well as consideration of benefits and risks whilst on antithrombotic treatment versus off treatment, allows the best current estimate of risks and benefits of warfarin, as well as that of aspirin which was also tested in three of these trials (AFASAK, SPAF-I, SPAF-II) [19, 46] (Table 2).

There were different target therapeutic ranges for the International Normalised Ratio of the prothrombin time (INR) which were used in the five initial primary prevention trials; these ranged between 1.5 and 4.5 (Table 2). However, the minimum risk of stroke appeared to occur in the INR range 2.0 to 3.0 [19, 46], which is now generally accepted as the optimum therapeutic range for anticoagulant prophylaxis of thromboembolism in all patient groups. Exceptions include those patients with older mechanical prosthetic heart valves, and those with recurrent thromboembolism (despite warfarin prophylaxis at INR 2.0–3.0, who require a higher intensity warfarin regimen (INR 3.0–4.5)). A target INR of 2.0 to 3.0 is therefore the recommended intensity of anticoagulation in the absence of the above indications for high intensity warfarinisation.

In the pooled analysis by the Atrial Fibrillation Investigators of the five initial primary prevention trials,

Table 2 Randomized trials of anticoagulation in atrial fibrillation

	<i>AFASAK</i> [17]	<i>SPAF-I</i> [18]	<i>SPAF-II</i> [44]	<i>BAATAF</i> [41]	<i>CAFA</i> [42]	<i>SPINAF</i> [43]	<i>EAF</i> [45]
Comment	warfarin <i>vs</i> aspirin 75mg <i>vs</i> placebo	warfarin <i>vs</i> aspirin 325 mg <i>vs</i> placebo	warfarin <i>vs</i> aspirin 325 mg	warfarin <i>vs</i> placebo	warfarin <i>vs</i> placebo	warfarin <i>vs</i> placebo; blinded study	warfarin <i>vs</i> aspirin 300 mg; <i>vs</i> secondary prevention study
Number	1007	1330	1100	420	383	571	1007
Mean age (years)	74	67	≤75 gp: 64 >75 gp: 80	68	68	67	73
Males (%)	54	71	≤75 gp: 76 >75 gp: 59	72	75	100	54
Target INR	2.8–4.2	1.7–4.6	2.0–4.5	1.5–2.7	2.0–3.0	1.5–2.8	2.5–4.0
Mean followup (years)	1.2	1.3	2.3	2.2	1.3	1.7	2.3
Ischaemic stroke %/year			≤75 >75 gp				
placebo	5.5	6.3	— —	3.0	4.6	3.9	12.0
warfarin	2.2	2.3	1.8 4.3	0.4	2.5	1.0	4.0
aspirin	4.7	3.6	1.4 4.6	—	—	—	10
Risk reduction							
warfarin	58%	67%	n/a	86%	37%	79%	66%
aspirin	32%	42%		—	—	—	—

[AFASAK = Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study; SPAF = Stroke Prevention in Atrial Fibrillation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation Study; SPINAF = Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation study; EAF = European Atrial Fibrillation Trial]

an annual rate of stroke of 4.5% was found in the control group and a rate of 1.4% in the warfarin group; this difference represents an overall risk reduction of 68% (95% confidence intervals 50% to 79%) [19]. Warfarin prophylaxis also resulted a similar risk reduction in stroke with residual deficit, a decrease in mortality by 33%, and a decrease in the combined adverse outcome (stroke, systemic embolism or death) by 48% [19]. Despite these impressive figures, the optimal efficacy of warfarin prophylaxis was probably underestimated, because most strokes in patients randomised to warfarin occurred whilst the patients were not in fact taking warfarin or were significantly under-anticoagulated at the time of the event [46].

The main problem with warfarin prophylaxis is the risk of bleeding, especially intracranial haemorrhage. The annual risks of intracranial haemorrhage increased from 0.1% in controls to 0.3% in warfarin groups in the pooled analysis, which represents an excess of two intracranial bleeds per annum per thousand patients treated [19]. This bleeding risk was particularly associated with an INR greater than 3.0, and with uncontrolled hypertension [19, 46]. A non-significant association with increasing age was also found [19, 46]. In the SPAF-II study, the benefits of warfarin were nearly counteracted by an increased risk of intracranial haemorrhage in the warfarin group, which was unexpectedly high in patients greater than age 75 years (1.8%/year); however, the rate of intracranial haemorrhage in this group was substantially higher than that reported in the

original five trials (on average 0.3%/years), which may reflect the higher intensity of anticoagulation in the SPAF-II study [19, 44]. The upper range for anticoagulation intensity in the latter study was an INR of 4.5, and an analysis of patients who did sustain intracranial haemorrhage found that most of those patients had an INR >3.0 (GW Albers, personal communication). Lower intensity warfarin (for example, target INR 1.5–2.5) is currently being compared directly with higher intensity warfarin in the SPAF-III study. Although the results are still awaited, some physicians use this regimen in patients for whom the 'usual' intensity of anticoagulation (target INR 2.0–3.0) is felt to carry an unacceptable risk of bleeding.

Despite the convincing evidence for the effectiveness of warfarin prophylaxis, which appears to substantially outweigh the risk of intracranial bleeding, concern has been expressed that the efficacy of warfarin in clinical trials may not translate into effectiveness in practice [9, 47, 48]. These trials were also never designed to provide anything more than an estimate of treatment efficacy, and although widely interpreted as being studies of warfarin treatment, these trials have been described as 'packages of care' that included drugs, monitoring and followup [9]. For example, patients in these trials were highly selected, especially for contraindications to warfarin, and on average less than 10% (range 3–40%) of eligible patients were randomised. In addition, many patients were excluded after initial assessments for the absence of contraindications and physicians' refusal to

enter their patients into the study. Recruitment of these patients was therefore primarily from hospital practice, self referral and referrals from interested physicians, suggesting that the populations were not representative of 'true' patients with atrial fibrillation in the community [9]. Furthermore, the frequent monitoring of warfarin therapy under trial conditions was probably more intense than that applied in usual clinical practice. For example, monitoring was performed at least every 3–4 weeks in the trials that reported frequency, and between 0.6% and 15% of the tests showed the anticoagulant effect to be greater than intended [17, 18, 41, 42, 45]. Hence, the ratio of antithrombotic benefit to bleeding risk may be lower in usual clinical practice than in published trials; and this may also reduce its cost-effectiveness [49]. Furthermore, a recent survey of patients with atrial fibrillation in a health maintenance organisation in the United States found a higher prevalence of concurrent illness, a less frequent monitoring interval, and a lower frequency of INR tests within the target therapeutic range, when compared to patients in clinical trials [47]. However, a study using decision analysis techniques demonstrated that the likely benefit of warfarin to all patients with atrial fibrillation was substantial in clinical practice [50]. Warfarin (as discussed above) reduces the risk of stroke and thromboembolism by two-thirds, but increases bleeding by 53% (or 0.5% per year). Since the initial risk of bleeding is five-fold smaller than the risk of embolism, prophylaxis with warfarin should be given unless it is considered that the risk of bleeding is perceived to be over six times more detrimental than the risk of thromboembolism [50].

The concerns about the risk-benefit ratio of warfarin prophylaxis in usual clinical practice, as well as the large work-load which regular monitoring of warfarin entails, have led investigators to ask four further questions. First, what is the relative efficacy of antithrombotic prophylaxis with platelet inhibitors, such as aspirin or ticlopidine (which does not require laboratory monitoring and which carries a lower bleeding risk), compared with warfarin in atrial fibrillation? Second, which subgroups of patients with atrial fibrillation have the highest risk of thromboembolism in the absence of antithrombotic prophylaxis, in whom the risks of bleeding and tedium of monitoring with warfarin prophylaxis may be most justified? Third, which other subgroups can be defined in whom aspirin prophylaxis appears as effective as warfarin (but with less hassle, cost and risk)? Finally, can subgroups be defined in whom the risk of thromboembolism is so low that neither aspirin nor warfarin thromboprophylaxis is required?

Aspirin prophylaxis in atrial fibrillation

Aspirin has been evaluated as primary thromboprophylaxis against stroke and thromboembolism in atrial fibrillation in two randomised trials compared against patients on no antithrombotic treatment [17, 18] and in one randomised trial against warfarin [44] (Table 2).

Table 3 Stroke risk in patients with atrial fibrillation, stratified by risk, with and without antithrombotic prophylaxis (Risk in % per patient-year)

<i>Antithrombotic therapy</i>	<i>None</i>	<i>Aspirin</i>	<i>Warfarin</i>
<i>High risk</i>			
(a) Previous stroke or TIA	12%	10%	4–5%
(b) Age 75+ years, other clinical risk factors (diabetes, hypertension)	8%	4–5%	1–2%
<i>Moderate risk</i>			
(a) Age under 65 years, other clinical risk factors (diabetes, hypertension)	3–4%	1–2%	1–2%
(b) Age 65–75 years			
(c) Age 75+, no clinical risk factors			
<i>Low risk</i>			
Age under 65 years, no clinical risk factors	1%	—	—

(data adapted from Atrial Fibrillation Investigators. *Arch Intern Med* 1994; **154**: 1449–1457; reproduced from reference 52, with permission)

Doses of aspirin used ranged from 75 mg in the AFASAK study [17] to 325 mg in the SPAF study [18, 44]. In addition, 46% of patients in placebo group of the BAATAF study were allowed to take aspirin 325 mg daily, with no beneficial effects found [51]. On treatment analysis showed that aspirin was only about half as effective as warfarin [19, 46]; however, the annual risk of stroke appears low in moderate risk patients treated with aspirin (Table 3); and as noted above aspirin is simpler to monitor and has a lower bleeding risk. Importantly, aspirin had no significant effect on severe strokes or mortality; although in the pooled analysis, aspirin did reduce the combined outcome of stroke, embolism or death by 28% [19]. In the EAFT study, aspirin was also less effective than warfarin when used as secondary prophylaxis in patients with previous stroke or transient ischaemic attack [45] (Table 3).

Risk stratification for antithrombotic prophylaxis in atrial fibrillation

The relative risk of stroke in persons with atrial fibrillation (and hence the absolute benefits of antithrombotic prophylaxis with warfarin or aspirin) vary greatly with the presence of other risk factors for stroke and thromboembolism. The risk of stroke in non-rheumatic atrial fibrillation appears similar in men and in women; and in persons with continuous atrial fibrillation compared to those with paroxysmal atrial fibrillation [19]. The largest available analysis of such risk factors comes from pooled analyses, from which data is summarised in Table 3 [19, 46, 52]. Again, it should be emphasised that the risk stratification in the pooled analyses was a *post hoc* subgroup analysis done on the low proportion (~10%) of subjects eligible for the trials.

Ideally, risk subgroups should be best studied on a whole natural population, but the results do provide some measure of risk stratification. Depending on associated risk factors, individual patients with atrial fibrillation could thus be considered as high, moderate or low risk for stroke and thromboembolism [52].

The *highest risk* of stroke was observed in persons with previous transient ischaemic attack (TIA) or stroke. In the pooled analysis of warfarin trials, the annual risk of stroke was 12% in controls and 5% in warfarin groups [19]. These results are similar to those in the randomised controlled trial of secondary prophylaxis in patients with a previous stroke and TIA, in which the annual risk of stroke was 12% in controls and 4% in warfarin groups [45]. Hence, in general warfarin is more effective in absolute terms as secondary prophylaxis than as primary prophylaxis; and also appears more effective than aspirin (Table 3). The pooled analysis of warfarin trials in atrial fibrillation showed that, in addition to a previous history of thromboembolism, independent risk factors for thromboembolism were increasing age, diabetes mellitus and history of hypertension [19]. These findings were not surprising, because these variables are known to be major risk factors for stroke in patients in sinus rhythm. The combination of age 75 years or over with diabetes or hypertension also indicates a high risk group, in whom warfarin prophylaxis appears highly effective (annual risk of stroke 8% in controls and 1–2% on treatment with warfarin; Table 3) [19, 46].

A *moderate risk* of stroke exists in persons with non-rheumatic atrial fibrillation, without previous cerebrovascular events or thromboembolism; those who are aged under 65 years with a history of diabetes or hypertension; those who are aged 65–74 (with or without a history of diabetes or hypertension); and those aged 75 years or more with no history of diabetes or hypertension. In these patients, aspirin appears to be as effective as warfarin, with a reduction in the annual risk of stroke from 4% to 1–2% [19, 46] (Table 3).

A *low risk* of stroke (annual risk 1%) exists in persons with non-rheumatic atrial fibrillation who are aged under 65 years who have no history of previous embolism, hypertension or diabetes. In such persons, antithrombotic prophylaxis with either aspirin or warfarin does not appear to be warranted unless some other indication or co-existing risk factor is present [19, 46] (Tables 3,4).

Role of echocardiography

The role of echocardiography in risk stratification in non-rheumatic atrial fibrillation remains unclear. Two studies found an increase in stroke risk in the presence of a large left atrium, impaired left ventricular function, or mitral valve calcification [25, 41]; however, whether or not echocardiographic risk factors add to the clinical risk stratification given alone is at present unknown. Transoesophageal echocardiography may be more sensitive for identifying predictors of stroke risk in atrial fibrillation patients, but its clinical importance in risk

stratification awaits confirmation. Anecdotally, however, increased risk of systemic embolism has been observed in patients with atrial fibrillation associated with heart valve disease (e.g. rheumatic); heart valve prosthesis, heart failure, intracardiac thrombus, or thyrotoxicosis [53–55]. On this evidence, as well as the evidence for antithrombotic efficacy of warfarin in non-rheumatic atrial fibrillation, it seems reasonable to advocate warfarin prophylaxis for such patients.

One possible algorithm for risk stratification and selection of prophylaxis in patients with atrial fibrillation is shown in Figure 1 [52]. This algorithm proceeds through history taking and clinical examination (which may indicate the need for warfarin thromboprophylaxis without recourse to echocardiography) prior to consideration of echocardiography, thus reducing the costs of routine echocardiography. In any case, echocardiography may be underutilised in risk stratification of atrial fibrillation [56]. A summary of the most recent recommendations of Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy on the use of antithrombotic therapy in atrial fibrillation is also provided in Table 4 [57].

Anticoagulation and cardioversion of atrial fibrillation

Anticoagulation in patients for cardioversion requires special discussion. It has been estimated that peripheral emboli may complicate external cardioversion in 1–3% of cases [58]. Thromboembolism following pharmacological cardioversion of atrial fibrillation may well have similar rates [59]. Anticoagulant therapy is therefore advised in the cardioversion of such patients despite the absence of prospective randomised trials on the effectiveness of such therapy [59]. The risk of embolism continues even after successful cardioversion as atrial mechanical function may not be restored for several weeks [59–61]. The optimal duration of anticoagulation is, as yet, unclear. Recent recommendations by the American College of Chest Physicians include: (i) the administration of warfarin for 3 weeks before elective cardioversion of atrial fibrillation of >2 days' duration; (ii) continuation of warfarin therapy for 2–4 weeks after

Table 4 Summary of antithrombotic therapy use in atrial fibrillation Recommendations of 4th American College of Chest Physicians Consensus Conference on Antithrombotic Therapy [53]

Age (years)	Risk factors*	Recommendation
age < 65	Risk factors present	— warfarin INR 2.0–3.0
	No risk factors present	— aspirin or nothing
age 65–75	Risk factors present	— warfarin INR 2.0–3.0
	No risk factors present	— warfarin or aspirin
age > 75		warfarin INR 2.0–3.0

* Risk factors are previous transient ischaemic attack or stroke, hypertension, heart failure, diabetes, clinical coronary artery disease, mitral stenosis, prosthetic heart valves or thyrotoxicosis.

cardioversion; (iii) administration of intravenous heparin followed by warfarin if cardioversion cannot be postponed for 3 weeks; and (iv) no anticoagulant therapy for atrial fibrillation of <2 days' duration or in cardioversion of supraventricular tachycardia, although atrial flutter should be managed similarly to atrial fibrillation [57].

Practical considerations in antithrombotic prophylaxis for atrial fibrillation

It is important to balance the risks (especially bleeding) and benefits in the individual patient, prior to starting antithrombotic prophylaxis with warfarin or aspirin. Possible factors which may increase the risk of bleeding whilst on warfarin include the following: age, uncontrolled hypertension (defined as systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg), alcohol excess, liver disease, poor drug or clinic compliance, and bleeding lesions (especially gastrointestinal blood loss, for example, peptic ulcer disease; or previous cerebral haemorrhage) or bleeding tendency (including coagulation defects and thrombocytopenia). Concomitant use of aspirin with oral anticoagulants also increases the risk of bleeding although this combination is currently being assessed in controlled trials. As noted above, current evidence favours a target INR of 2.0–3.0, although some physicians target a lower range of INR (1.5–2.5) in patients at increased risk of bleeding. To minimise the risk of intracranial bleeding on prophylactic warfarin, hypertension should be adequately controlled and closely monitored [46]. The risks and benefits of warfarin should also be reviewed annually, especially in patients aged over 80 years.

Intracranial haemorrhage should be excluded, for example, by computed tomography scanning, in patients with acute stroke and atrial fibrillation before commencing warfarin. This is an important consideration as 11% of patients with haemorrhagic stroke have atrial fibrillation, compared to the frequency of 18% in stroke due to cerebral infarction [12]. When and whether or not to start anticoagulation after an acute cardioembolic stroke poses another problem, as there is a risk of haemorrhagic transformation of the cerebral infarct, by bleeding into the infarcted, softened brain. Recent recommendations by the American College of Chest Physicians are the following: (i) patients with small or moderate cardioembolic strokes in whom an intracranial bleed is excluded by CT scanning at 48 h should be started on heparin followed by warfarin (INR 2.0 to 3.0); (ii) in patients with large cardioembolic strokes or uncontrolled hypertension, anticoagulant therapy should be postponed for 5–14 days, because of the increased risk of haemorrhagic transformation [62]. In patients with atrial fibrillation as the presumed cause of thromboembolism, initiation of warfarin therapy (after CT scanning at 48 h) without initial heparin therapy is reasonable in view of the relatively low risk of early recurrent thromboembolism [62].

Patients who are anticoagulated longterm require to

be regularly followed up in anticoagulant clinics to optimise anticoagulant control, thus imposing some restriction on their lives. There have been concerns that service provision for the use of anticoagulants in atrial fibrillation may be insufficient, particularly with the need for caution in interpreting the results of the large studies and extrapolating these results to the British population [9]. Patients on warfarin also need education about their therapy and they must regularly have blood tests, since the effect of warfarin must be regularly monitored and the dose adjusted. General practitioners looking after such patients also need to be aware of potential drug interactions and risks in such patients.

In the BAATAF study, no significant differences between warfarin-treated patients and controls were found for quality of life as demonstrated by measures of functional status, well-being, and health perceptions; unless complicated by a bleeding episode [63]. Surprisingly, the quality of life assessment of patients in the BAATAF study demonstrated that 76% did not mind regular blood tests [63]. Patients on warfarin who sustain a bleeding complication demonstrate a significant decrease in health perceptions [63].

It should be noted that primary prophylaxis with anticoagulant therapy in atrial fibrillation is cost effective if the rate of intracranial bleeding during such therapy is only 0.3%, as in the major published trials [49]. However, if this rate increases to 2% per year, warfarin therapy becomes no longer cost effective. This emphasises the importance of careful patient selection for warfarin prophylaxis, regular monitoring and control, and regular review of the balance of risks and benefits. Thus, in high risk patients in whom warfarin is judged to be contra-indicated, aspirin prophylaxis may be appropriate. Whatever prophylaxis is given, however, risk factors should be reviewed annually because they change: for example, the risk of stroke increases with age (Figure 1).

Further approaches to prophylaxis

The combined effects of aspirin plus warfarin have not been established, although this is currently being investigated for high risk groups in the SPAF-III study. Treatment strategies with low risk and high practicality are also needed. The potential of low-intensity warfarin has been noted. Ultra-low dose warfarin therapy (e.g. 1 mg daily) can successfully prevent thrombus formation in central venous catheters without any detectable change in INR levels or risk of bleeding [64]. Similarly such a low-dose anticoagulation regimen reduces the risk of thromboembolism in patients with malignancy [65]. These studies suggest that ultra-low dose warfarin (1 mg daily) may affect the *in vivo* function of Vitamin K coagulation factors in ways not detectable by conventional assays such as the INR. However, whether or not such an ultra-low dose regime is suitable for patients with atrial fibrillation remains to be demonstrated. Studies are in progress investigating the potential of such a regimen.

Figure 1 Algorithm for risk stratification and use of warfarin or aspirin as thromboprophylaxis in atrial fibrillation

History taking and clinical examination (which may indicate the need for warfarin prophylaxis without recourse to echocardiography) is essential prior to consideration of echocardiography, thus reducing the requirement for routine echocardiography.

(risk stratification based on the pooled analysis of the Atrial Fibrillation Investigators [19] and the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy on the use of antithrombotic therapy in atrial fibrillation [57]; figure adapted from reference 52, with permission)

Practical problems in identification of patients at high and moderate risk of thromboembolism for prophylaxis

If warfarin and aspirin are established thromboprophylaxis in high and moderate risk patients with atrial fibrillation respectively, the problem remains to identify such patients with atrial fibrillation for prophylaxis. There is at present no easy way to stratify patients for baseline risk and potential benefit. Many such patients may be unrecognized and undiagnosed in the community, with few or no symptoms. Formal screening for atrial fibrillation in primary care would also have to be considered, with considerable implications not only for general practice but for cardiological assessments and investigations (such as echocardiography) and the inconvenience and costs of introducing and monitoring anticoagulation. Whilst there is some evidence that anticoagulant monitoring by general practitioners is as effective as hospital-based services, not all general practitioners would be prepared to take on the responsibility of monitoring warfarin without further resources [66]. Perhaps better identification of hospital admissions with atrial fibrillation and their risk stratification whilst in hospital is required. For example, in a recent prospective survey of acute medical admissions to a district general hospital 6.3% had atrial fibrillation, but there was a surprisingly low rate of antithrombotic therapy use; of the 102 patients with atrial fibrillation who were identified over a 6 month period, only 20 were taking warfarin and 17 were taking aspirin, and anticoagulation was given to only 7 of the 150 patients who had not previously been taking warfarin [56]. The retrospective audit by Bath *et al.* [67] also found that many patients with atrial fibrillation were not prescribed warfarin despite the absence of contraindications. The ability to select out patients at high risk of stroke and thromboembolism (Figure 1) is therefore highly relevant in clinical practice. Reasons often cited for the lack of anticoagulant prophylaxis include the fear of complications, inconvenience, lack of perceived importance of thromboemboli and lack of manpower resources.

Recent studies point towards the existence of a hypercoagulable state in patients with atrial fibrillation [68]. Cross-sectional studies have shown high plasma levels of fibrinogen (a strong risk factor for thrombosis, including stroke), fibrin D-dimer (a marker of fibrin turnover and thrombogenesis) and von Willebrand factor (a marker of endothelial disturbance) in such patients [69–71]. The value of these markers in prediction of thrombosis and death has been demonstrated in patients with peripheral vascular disease [72] and in normal subjects [73, 74]. Introduction of oral anticoagulant therapy [71] or cardioversion to sinus rhythm [75] has been shown to normalise the raised levels of plasma fibrin D-dimer levels (but not fibrinogen or von Willebrand factor levels) in patients with atrial fibrillation, which is consistent with the thromboprophylactic benefits of warfarin. Prospective studies on the predictive value of these thrombotic markers for thromboembolic events in patients with atrial fibrillation deserve to be performed to see if they can refine risk stratification. Measurement of fibrin D-dimer levels also

offer potential monitoring of efficacy of antithrombotic prophylaxis.

Conclusion

There is now good evidence that antithrombotic prophylaxis with long-term warfarin or aspirin is effective in reducing thromboembolic risk in high- and moderate-risk patients with atrial fibrillation, and the identification, risk assessment and regular review of such patients should be practiced routinely by general practitioners and hospital practitioners. Risk stratification in atrial fibrillation is easily performed on clinical grounds: echocardiography and (perhaps in the future) laboratory measures of hypercoagulability may help refine risk stratification.

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