Non-valvular atrial fibrillation and stroke prevention

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Abstract

Atrial fibrillation (AF) affects 5% of people older than 65 years. Among patients with AF, the risk of stroke is about 5% per year. The risk of stroke increases cumulatively with increasing age, previous transient ischaemic attack or stroke, hypertension, diabetes, impaired left ventricular function and a large left atrium.

Management aims to identify and treat the underlying cause, control the ventricular rate, restore and maintain sinus rhythm, and minimise the risk of stroke. Warfarin reduces the risk of stroke by about two-thirds, and aspirin by about one-fifth. The risk of anticoagulant-associated haemorrhage increases with serious concomitant disease, and with poorly controlled hypertension and poorly controlled anticoagulation.

All patients with chronic AF should be considered for oral anticoagulant therapy, and the decision based on the balance between the risks of thromboembolism and bleeding. The recommended INR (international normalised ratio) is 2.0-3.0. Treating 1000 "average" AF patients (i.e., those with a 5% per year risk of stroke) with warfarin prevents about 30 strokes and causes at least two episodes of major haemorrhage each year. Treating 1000 AF patients with aspirin prevents about 15 strokes each year.

The prevalence of AF increases with age, from about 2% in the general population to 5% in people older than 65 years, and 10% in people older than 75 years. It may occur as a single episode, a series of recurrent episodes ("paroxysmal" AF), or continuously ("permanent", or "chronic" AF).

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Atrial fibrillation (AF) affects 5% of people older than 65 years. Among patients with AF, the risk of stroke is about 5% per year. The risk of stroke increases cumulatively with increasing age, previous transient ischaemic attack or stroke, hypertension, diabetes, impaired left ventricular function and a large left atrium. Management aims to identify and treat the underlying cause, control the ventricular rate, restore and maintain sinus rhythm, and minimise the risk of stroke. Warfarin reduces the risk of stroke by about two-thirds, and aspirin by about one-fifth (1). The risk of anticoagulant-associated haemorrhage increases with serious concomitant disease, and with poorly controlled hypertension and poorly controlled anticoagulation. All patients with chronic AF should be considered for oral anticoagulant therapy, and the decision based on the balance between the risks of thromboembolism and bleeding. The recommended INR (international normalised ratio) is 2.0-3.0. Treating 1000 "average" AF patients (i.e., those with a 5% per year risk of stroke) with warfarin prevents about 30 strokes and causes at least two episodes of major haemorrhage each year. Treating 1000 AF patients with aspirin prevents about 15 strokes each year (1).

AF is a common arrhythmia. Its prevalence increases with age, from about 2% in the general population to 5% in people older than 65 years, and 10% in people older than 75 years. It may occur as a single episode, a series of recurrent episodes ("paroxysmal" AF), or continuously ("permanent", or "chronic" AF).

AF is an important arrhythmia because it may signify an underlying heart disease, it may cause symptoms of decreased cardiac output (e.g., malaise, effort intolerance) or palpitations, and it is associated with an increased risk of systemic thromboembolism and stroke. This risk of stroke averages about 5% per year among all individuals in AF, which is about 5-6 times greater than for people of the same age who are in sinus rhythm.

The management of AF has four principal objectives:

- To confirm and document the arrhythmia;
- To identify and treat the underlying cause;
- To relieve symptoms of decreased cardiac output by controlling the ventricular rate and restoring and maintaining sinus rhythm;
- To reduce the risk of systemic thromboembolism, particularly stroke.

All patients, except perhaps the very elderly and infirm, should undergo investigation for underlying causes of AF, including thyroid function tests and echocardiography. In haemodynamically stable patients, β-blockade, verapamil or diltiazem can be used to control the heart rate (E4). Recent-onset AF reverts spontaneously within 24 hours in at least half of patients (irrespective of whether or not they are taking digoxin). Patients who have been in AF for more than 48 hours should be considered for anticoagulation therapy and strategies to restore and maintain sinus rhythm. Warfarin should be administered for three weeks before cardioversion is attempted. If cardioversion can not be postponed for three weeks, the patient should undergo anticoagulation therapy with intravenous heparin and warfarin, and be considered for transoesophageal echocardiography (TOE). Cardioversion can probably be undertaken safely (with limited risk of stroke) if TOE excludes left atrial and appendage thrombus (and the patient is treated with heparin and warfarin). However, if transoesophagealechocardiography identifies left atrial and appendage thrombus, then cardioversion is contraindicated until the patient has been anticoagulated for at least three weeks. The relative merits of cardioversion by electrical shock and medical therapy have been discussed recently. Direct current cardioversion has never been subjected to a randomised trial, but appears to be the most effective method of restoring sinus rhythm. Its main disadvantage is the need for general anaesthesia. Digoxin and verapamil are ineffective for converting AF to sinus rhythm. Flecainide or sotalol are the preferred medical therapies in younger patients without structural heart disease, and amiodarone in older patients. The

chances of successful cardioversion are greater if the AF is of recent onset and the left atrial size is normal. After successful cardioversion, warfarin therapy should be continued for at least four weeks to prevent clot formation in the "stunned" left atrium. Antiarrhythmic drug therapy should also be continued to prevent recurrent AF, but this still occurs in 40-50% of patients after 12 months' follow-up despite drug therapy. If the patient has a low risk of recurrence of AF (e.g., "lone" AF) and remains in sinus rhythm for one month after cardioversion, anticoagulation therapy with warfarin can be ceased. In patients at higher risk of recurrence, it may be more appropriate to continue warfarin therapy for longer or indefinitely. For patients who are elderly (in whom AF is usually chronic and antiarrhythmic drug therapy may be risky) or have asymptomatic chronic AF, it is often reasonable to avoid attempted cardioversion, accept the AF and aim for adequate ventricular rate control (digoxin combined with â-blockade, verapamil or diltiazem) and long term anticoagulation therapy. The results of clinical trials in patients with asymptomatic AF (of rate control and antithrombotic therapy versus attempted cardioversion and maintenance of sinus rhythm to avoid warfarin) are awaited. Strategies for reducing the risk of stroke and systemic thromboembolism in patients with AF have been studied in several randomised controlled trials over the past decade.

Warfarin versus control

Primary prevention

Five large randomised controlled primary prevention trials have shown that, in people with chronic non-valvular AF, warfarin reduced the risk of stroke by about two-thirds (68%; 95% CI, 50%-79%; P<0.001), from about 4.5% to 1.4% per year overall, with little increase in frequency of major bleeding (warfarin, 1.2%; control, 1.0%), or intracranial haemorrhage (warfarin, 0.3% per year; control, 0.1% per year). This means that warfarin will prevent about 30 strokes per 1000 patient-years of treatment at a cost of at least two serious bleeding episodes per 1000 patients treated for one year. It must be stressed, however, that this acceptable rate of bleeding was achieved in patients who were carefully selected, screened and closely followed; 53%-93% of eligible patients with AF were not included in the trials because of an increased risk of bleeding. Exclusion criteria included old age (>75 years), serious illness (liver, kidney, brain or malignant disease), alcoholism, fall risk (e.g., syncope), forgetfulness, non-steroidal anti-inflammatory drug therapy, and uncontrolled hypertension.

Secondary prevention

One secondary prevention trial (the European Atrial Fibrillation Trial [EAFT]) showed that, in people with chronic non-valvular AF and symptoms of previous transient ischaemic attack (TIA) or stroke, who have a risk of stroke of 12% per year, warfarin therapy (target INR, 2.5-4.0) reduced the risk of stroke by about two-thirds (66%; 95% CI, 53%-80%), to 4% per year The annual incidence of major bleeding complications was 2.8% in the anticoagulant group and 0.7% in the placebo group. No intracranial bleeds were identified in patients assigned to warfarin. Thus, warfarin prevents about 80 strokes per 1000 patient-years in patients who have had a TIA or stroke and who are in AF, at a cost of at least 20 serious bleeding episodes per 1000 patients treated for one year.

The timing of anticoagulation therapy after recent ischaemic stroke depends on the risk of recurrent thromboembolism and the risk of haemorrhagic transformation of the brain infarct (which is higher within the first two weeks and in patients with large brain infarcts and uncontrolled hypertension. Common empirical practice is to treat patients with fibrillating acute ischaemic stroke immediately with aspirin (300 mg daily) and then, depending on the above factors, begin warfarin (5 mg daily) between days three and 14 after stroke onset, aiming to achieve an INR of 2.0. However, randomised trials comparing aspirin with heparin during the first two weeks of acute

ischaemic stroke among patients in AF show no benefit from early anticoagulation, because any net gains from reduction in recurrent ischaemic stroke are offset by the excess hazards of haemorrhagic stroke (1).

Aspirin versus control

Three primary prevention and three secondary prevention trials have shown that, in people with AF, aspirin reduced the incidence of stroke by 22% (95% CI, 2%-38%), from 5.2% (placebo) to 3.7% (aspirin) per year for primary prevention (absolute risk reduction: 1.5% per year), and from 12.9% (placebo) to 10.4% (aspirin) per year for secondary prevention (absolute risk reduction, 2.5% per year).

Aspirin was not associated with any significant excess of intracranial haemorrhage (aspirin, 0.16%; control, 0.13%) or major extracranial bleeding (aspirin, 0.5%; control, 0.6%). This means that aspirin might prevent about 10 to 20 strokes per 1000 patient-years of treatment, depending on the type of patient treated and their baseline risk of stroke, with little risk of major bleeding. A speculative interpretation of these data is that, in patients with AF, aspirin prevents strokes due to atherothromboembolism, but not cardiogenic embolism. This interpretation is based on the magnitude of the effect (a 20% relative risk reduction), which is very similar to the effect of aspirin in patients with symptomatic atherothromboembolism of the brain, heart and limbs. Whether aspirin combined with adjusted-dose warfarin would be safe and more effective (in preventing both athero-thrombotic and cardiogenic strokes) than warfarin alone in patients with AF remains unknown (2).

Warfarin versus aspirin

The relative benefits and risks of warfarin and aspirin have been studied in three trials, all of which showed that warfarin was associated with half the risk of stroke compared with aspirin (47% relative risk reduction; 95% CI, 28%-61%; P<0.01).

Warfarin combined with aspirin

For patients with AF who are at high risk of stroke, adding aspirin (325 mg daily) to low-intensity, fixed-dose warfarin, adjusted to an INR of 1.2-1.5, was not as effective in preventing stroke or systemic thromboembolism as standard adjusted-dose warfarin therapy, maintaining an INR of 2.0-3.0 (event rates, 7.9% per year v. 1.9% per year, respectively; P<0.0001), and there is no difference in the rates of major bleeding .Three subsequent trials also suggested that adjusted-dose warfarin (INR, 2.0-3.0) was superior to low-intensity anticoagulant therapy or an aspirin- anticoagulation regimen (3).

Warfarin versus other antiplatelet agents

An Italian study reported that a new antiplatelet agent, indobufen (100-200 mg twice daily), was as effective as adjusted-dose warfarin (INR, 2.0-3.5) in preventing stroke, systemic embolism myocardial infarction or vascular death in 916 patients with non-valvular AF and recent (within 15 days) TIA or non-disabling ischaemic stroke. The 12-month event rates were 10% in the warfarin group and 12% in the indobufen group (P=0.47). However, the number of patients and outcome events were quite small, follow-up was short, and it is possible that a true difference was not detected.

Future studies are planned to evaluate the safety and effectiveness of other, newer antiplatelet agents (such as clopidogrel, oral glycoprotein IIb/IIIa receptor inhibitors, and oral thrombin inhibitors) and combination antiplatelet therapies (such as aspirin-ticlopidine, aspirin-clopidogrel, and aspirin-dipyridamole) as strategies of thromboprophylaxis in AF (4).

Not all patients with AF benefit from thrombo-prophylactic treatment. The decision to treat depends on the balance between the risk of thromboemboli without treatment and the risks of thromboemboli and haemorrhage with treatment in each patient, as well as the patient's willingness to accept the potential risks, costs, and inconvenience of treatment in order to possibly benefit. The current profile of individual risk of thromboembolism and bleeding complications (see below) remains imprecise and continues to be refined as new data emerge (5). The important independent prognostic factors for an

increased risk of stroke among individuals with AF are increasing age, a history of previous TIA or stroke, hypertension, diabetes mellitus, and transthoracic echocardiographic evidence of moderate to severe left ventricular systolic dysfunction. Echocardiographic evidence of left atrial enlargement and left atrial spontaneous echo densities ("smoke"), possibly indicative of stasis of blood, are also significant risk factors for stroke. These risk factors are cumulative: for people younger than 65 years with no risk factors the untreated annual risk of stroke is about 1%, whereas with one or more risk factors it is about 5%; for people aged 65-75 years with no risk factors the annual risk of stroke is about 4%, and with one or more risk factors it is about 6% per year; and for people older than 75 years with no risk factors the risk of stroke is about 3%-4%, whereas with one or more risk factors it is about 8% (6).

Who is at high risk of haemorrhage with anticoagulant treatment?

The major risk factors for anticoagulant-associated intracranial haemorrhage include fragile intracranial blood vessels (previous symptomatic cerebrovascular disease, computed tomography brain scan evidence of small vessel disease, "leukoaraioisis"), high blood pressure (poorly controlled hypertension), and excessive anticoagulation (INR, > 3.5) or factors predisposing to it, such as confusion, dementia, inadequate anticoagulant monitoring, alcoholic liver disease, and a tendency to falls. Increasing age is a risk factor for all of these risk factors, and is thus a potent risk factor for anticoagulant-associated haemorrhage (7). Among a subgroup of patients in the Stroke Prevention in Atrial Fibrillation (SPAF) II trial (mean age, 80 years), the rate of intracranial haemorrhage was as high as 1.8% per year in those allocated to warfarin therapy (target INR, 2.0-4.5) and 0.8% among those who were assigned to aspirin. Although the target INR in this study was higher than currently recommended (INR, 2.0-3.0), these data suggest that the low rate of intracranial haemorrhage documented in the five primary prevention AF trials may not apply to very elderly individuals (who were not well represented in many of these trials - the mean age of the patients studied in the AF trials was 69 years, and only about a quarter were older than 75 years) (8).

Recommendations for antithrombotic therapy for AF

Current practice necessitates individualisation of therapy after an integrated clinical assessment that evaluates thromboembolic risk due to AF, other potential indications for anticoagulant therapy, risk of haemorrhage, and non-medical factors relating to compliance, capacity to have the INR monitored at least monthly, gait instability, risk of other trauma, and patient values and preferences. Decision analysis can also be useful.

The role of transthoracic echocardiography (TTE), in addition to excluding structural heart disease in all patients who first present with AF, is to further refine stroke risk in the small group of patients with a low risk of stroke according to clinical factors. Although TOE is more sensitive in detecting left atrial thrombus and spontaneous echo contrast, which are markers for increased risk of thromboembolism, it is more invasive and is usually only required to improve risk stratification among individuals with a relative contraindication to warfarin or in whom TTE is inadequate. The choices of thromboprophylactic agents for atrial fibrillation include warfarin, which is the most effective but also the most risky treatment, and aspirin, which is less effective than warfarin but safer. The combination of aspirin and low dose warfarin is no more effective than aspirin alone. The most appropriate treatment regimen is one in which patients at high risk of stroke and low risk of haemorrhage are treated with warfarin, and patients at low risk of stroke or high risk of haemorrhage are treated with aspirin (9).

Individuals with AF who are aged less than 60 years and have no evidence of any concurrent heart disease have a very low risk of a thromboembolic event (about

0.6% per year).The potential benefits of aspirin in these patients (which may reduce the risk of stroke by 0.12% per year [20% of 0.6%]) may be offset by an equal potential risk of aspirin-associated haemorrhagic stroke of 0.12%.

Warfarin is indicated for individuals with chronic AF who are at high absolute risk of stroke (>4% per year), such as those with any of the independent thromboembolic risk factors listed above, and a lower risk of haemorrhage.

Similarly, anticoagulant therapy should also be considered in patients with paroxysmal AF, again depending on the thromboembolic risk factors as well as the frequency and duration of the paroxysms (10). Although clinical trial evidence suggests the stroke rate of patients with paroxysmal AF is similar to that of patients with chronic AF, the trials did not specifically examine the benefits of antithrombotic therapy in patients with paroxysmal AF. Furthermore, the range of thromboembolic risk in such patients is likely to be extremely wide, from very low for patients who have one short paroxysm once a year to considerably higher for patients who have daily lengthy paroxysms.

Conflicts of interest: None declared.

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