Atrial fibrillation and stroke prevention in elderly people

The prevalence and incidence of atrial fibrillation is increasing along with the geriatric population. Its association with stroke results in significant burden to the patient and to the NHS. Sequelae of atrial fibrillation could be avoided with recognition and appropriate prevention. This article reviews antiplatelet and anticoagulant treatments used for prevention of stroke in patients with atrial fibrillation, with reference to evidence for risk of bleeding, and discusses risk stratification for starting warfarin.

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Atrial fibrillation is an important risk factor for stroke, which increases with age. Patients older than 65 years with lone atrial fibrillation have a 5-fold increase in prevalence of ischaemic stroke. This condition is also becoming more common—the occurrence increased from 3·2% in men aged 65–84 years in 1968–70, to 9·1% in 1987–89.[1] 15–20% of all ischaemic strokes occur in patients with atrial fibrillation, and about 35% of such patients who do not receive anticoagulation will have a stroke.

The Stroke Prevention in Atrial Fibrillation (SPAF) study[2] showed that paroxysmal atrial fibrillation has similar rates of stroke to persistent atrial fibrillation. Additionally, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial[3] revealed that the rhythm-control group had the same incidence of stroke as the rate-control group in patients who were not on anticoagulant drugs. This article reviews anticoagulant and antiplatelet drugs used for prevention of stroke in atrial fibrillation, with reference to trials, risks of bleeding, and risk stratification for starting warfarin.

Aspirin is derived from salicylate, with anti-inflammatory, analgesic, antipyretic, and antithrombotic effects. It inhibits platelet aggregation by irreversible blockage of cyclooxygenase, resulting in inhibition of prostacyclin and thromboxane. Warfarin is a reversible competitive inhibitor of vitamin K, which results in hepatic synthesis of inactive clotting factors (ie, factors VII, IX, and X). It prevents formation of fibrin-rich thrombi predominantly seen in the deep veins and the left atrium. What trials have been undertaken with aspirin and warfarin, and what were the findings?

Primary prevention trials

The Atrial Fibrillation, Aspirin, Anticoagulation Study AFASAK[4] was a randomised, placebo controlled study that ran from 1985 to 1988. 1007 patients took aspirin 75 mg, warfarin (international rormalised ratio [INR] 2·8–4·2), or placebo. The reduction in strokes in people on warfarin was 64%, compared with placebo an absolute risk reduction of 3·5% per year ($p<0·05$). A non-significant decrease in the frequency of strokes was seen with aspirin 75 mg ($p=0·57$) compared with placebo. 21 patients on warfarin withdrew because of non-fatal bleeding complications, compared with two on aspirin, and none on placebo.

In the SPAF-I randomised trial,[2] 1330 people were categorised as eligible or ineligible for warfarin. In the eligible group, patients were randomly assigned to receive aspirin 325 mg, warfarin (INR 2·0–4·5), or placebo. In the ineligible group, patients were randomly assigned aspirin or placebo. The annual risk of ischaemic stroke was 2·3% in the warfarin group, and 7·4% in the placebo group. ($p=0·01$; risk reduction 67%). In all patients receiving aspirin, the annual risk of an ischaemic stroke was 3·6% ($p=0·02$; risk reduction 42%).

410 patients in the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)[5] were randomly assigned to warfarin (INR 1·5–2·7), or to no treatment. Patients in the control group could choose to take aspirin. The annual rate of stroke was 3·9% with aspirin and 0·45% with warfarin. The total mortality rates were 2·25% on warfarin group and 5·97% in the control group. Minor bleeding occurred in 38 patients in the warfarin group compared with 21 in the control group.

The Stroke Prevention in Nonrheumatic Atrial Fibrillation study (SPINAF)[6] assigned people to warfarin (INR 1·4–2·8) or to placebo. The annual event rate for patients older than 70 years was 4·8% for placebo, and 0·9% for warfarin (risk reduction 0·79; $p=0·02$). Major and minor haemorrhages were slightly more common in the warfarin group.

Secondary prevention trials

The European Atrial Fibrillation Trial (EAFT)[7] included 1007 patients with an average age of 71 years who had a history of transient ischaemic attack or stroke. Group 1

received warfarin (INR 2·5–4·0), aspirin 300 mg, or placebo. Group 2 was assigned aspirin 300 mg or placebo. The annual rate of outcome events (strokes, myocardial infarctions, systemic embolism) was 8% with warfarin and 17% with placebo (risk ratio [RR] 0·53). The risk of stroke was reduced from 12% to 4% per year (RR 0·34) on warfarin. Patients on aspirin had an annual incidence of outcome events of 15% versus 19% in those on placebo (RR 0·83). The incidence of major bleeding events was 2·8% per year with warfarin and 0·9% with aspirin.

In the SPAF-II study,[8] warfarin (INR=2·0–4·5) and aspirin (325 mg) in patients younger than 75 years, was compared against patients older than 75 years. 1100 patients were followed-up over 2·3 years. The event rates were 1·3% per year in the warfarin-treated group and 1·9% in the aspirin-treated group, for the younger patients (p=0·24). The event rates were 3·6% in the warfarin-treated group and 4·8% in the aspirin-treated group, for the older patients (p=0·39).

SPAF-III[9] was published in 1996. In this trial, 1044 patients were randomly assigned to warfarin (INR 2·0–3·0), or fixed-dose warfarin (INR 1·2–1·5) with aspirin (325 mg). Patients had a variety of risk factors, and the trial was stopped after a mean follow-up of 1·1 years. The annual incidence of ischemic stroke was 7·7% in the aspirin and warfarin group, and 1·9% in the adjusted-dose warfarin group (p<0·0001). The absolute reduction of ischaemic stroke with adjusted-dose warfarin was 6% per year (95% CI 3·4–8·6).

Warfarin versus aspirin

A meta-analysis of six trials by Hart and colleagues[10] in 1999 showed that warfarin reduced strokes by 62%. The absolute risk reductions were 2·7% per year for primary prevention, and 8·4% per year for secondary prevention. The absolute increase in extracranial bleeding with warfarin was 0·3% per year. Aspirin reduced strokes by 22%. Absolute risk reductions were 1·5% per year for primary prevention, and 2·5% per year for secondary prevention. The authors concluded that warfarin was more efficacious than aspirin, and that the benefits of anticoagulation therapy were not offset by major haemorrhage.

Another meta-analysis pooling six trials[11] suggested that patients receiving warfarin were less likely to have a stroke (2·4 versus 4·5 events per 100 patient-years; hazard ratio [HR] 0·55; 95% CI 0·43–0·71), but were more likely to have major bleeding (2·2 versus 1·3 events per 100 patient-years; HR, 1·71; 95% CI, 1·21–2·41). The reduction in ischaemic stroke risk was similar in patients with paroxysmal atrial fibrillation (1·5 versus 4·7 events per 100 patient-years; HR 0·32; 95% CI, 0·16–0·61; p<0·001). Treating 1000 patients who had atrial fibrillation with warfarin for 1 year rather than with aspirin would prevent 23 ischaemic strokes, and cause nine major bleeds. The authors concluded that warfarin decreased the rate of stroke compared with aspirin, but increased the absolute risk of bleeding.

The evidence suggests that warfarin is superior to aspirin for prevention of stroke, but has to be balanced with the risk of bleeding. Also, the SPAF-II trial has shown only a 0·5% risk of stroke in those younger than 75 years who have no other risk factors. The relative-risk reduction between aspirin and warfarin was 0·68. Thus, depending on the patient's history, aspirin may be more appropriate.

In the guidelines from the Royal College of Physicians,[12] patients who have had an ischaemic stroke should take aspirin 50–300 g, low-dose aspirin and dipyridamole, or clopidogrel 75 mg only. The NHS Clinical Knowledge Summaries[13] recommend warfarin in patients who have had a stroke with atrial fibrillation (high or moderate risk patients). For people unable to take warfarin, aspirin is suggested. A recomended dose is not given because the doses in trials vary, and evidence of efficacy is inconsistent. The American Heart Association suggests 325 mg.[14]

Aspirin and clopidogrel versus warfarin

Clopidogrel irreversibly blocks the adenosine disulphate receptor on platelet cell membranes, thus preventing platelet aggregation. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVEW)[15] aspirin and clopidogrel were compared with warfarin. 6700 patients were assigned to clopidogrel 75 mg plus aspirin 75–100 mg, or warfarin (INR 2·0–3·0). The primary outcome was stroke, systemic emboli, myocardial infarction, or vascular death. The trial was stopped at a median follow-up of 1·8 years—the annual risk for a primary end point with warfarin was 3·9%, and 5·6% with aspirin and clopidogrel (p=0·0003). Major bleeding was similar in the two groups (2·2% versus 2·4%), but warfarin was associated with significantly more hemorrhagic strokes (0·36% versus 0·12%) and fewer minor bleeds (11·5% versus 13·6%).

Ximelagatan

Ximelagatran is an oral direct thrombin inhibitor. It is a lipophillic molecule that is easily absorbed and converted to its active form, melagatran. It has a half-life of 4–5 hours, is taken twice daily, has fast onset and offset of action, and does not require INR monitoring.

In the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation trial (SPORTIF III),[16] researchers randomly assigned 3410 patients with atrial fibrillation to warfarin (INR 2·0–3·0) or ximelagatran (36 mg twice daily). In the 4941 patient-years of exposure, the primary event rate was 2·3% per year with warfarin and

1·6% per year with ximelagatran (relative risk reduction 29%, p=0·10). Major and minor haemorrhages were lower with ximelagatran (29·8% versus 25·8% per year; relative-risk reduction 14%, p=0·007) Raised serum alanine amino-transferase concentration was more common with ximelagatran. However, in 2006, AstraZeneca, the manufacturer of ximelagatran, removed it from sale citing reports of hepatotoxicity during trials.

Risk of bleeding versus optimum dose of warfarin

If warfarin has been shown to be superior in stroke prevention, what is the risk of bleeding, and what is the optimum dose? Hylek and colleagues[17] studied 74 inpatients with atrial fibrillation after an ischaemic stroke while on warfarin from 1989 to 1994. For each patient with stroke, three controls with atrial fibrillation were randomly selected from the anticoagulant-therapy unit (222 controls). The adjusted odds ratio for a stroke at INR 1·7, compared with an INR of 2·0, was 2·0 (95% CI, 1·6 to 2·4). At an INR of 1·3, the odds ratio was 6·0 (95 % CI, 3·6–9·8).

In another study by Hylek,[18] 121 patients with intracranial haemorrhage while on warfarin were each randomly matched to three controls. The study used Prothrombin Time Ratio (PTR), in which INR=PTR^{ISI} (ISI=International Sensitivity Index of the thromboplastin reagents). 77 patients had intracerebral haemorrhage and 44 had subdural haemorrhage. For each 0·5 increase in PTR, the risk of intracerebral haemorrhage doubled (odds ratio, 2·1; 95% CI 1·4–2·9). In subdural haemorrhage, the risk rose dramatically above a PTR of 2·0 (approximate INR 4·0). Age was the only other significant independent risk factor for subdural haemorrhage (OR 2·0 per decade; 95% CI 1·3–3·1).

Man-Son-Hing and colleagues[19] calculated the risk of intracranial bleeding from falls from prospective cohort studies and retrospective case series, and stroke-reduction benefit was taken from meta-analysis of 5 randomised controlled trials. The calculated risk of a subdural haematoma from falling in a patient with a 5% annual stroke risk; they would need to fall 295 times in a year for the fall risk to outweigh the stroke-reduction benefit of warfarin. In summary, an INR of 2·0–3·0 suggests appropriate anticoagulation in patients with atrial fibrillation. Age is a risk factor in intracranial bleeds, but tendency to fall is less of a risk.

Risk stratification

Risk factors for stroke include congestive heart failure, hypertension, age older than 75 years, diabetes, and impaired left ventricular function. In 1998, a study of 1066 patients from 3 different trials showed that moderate-to-severe function gave a 2·5% (p<0·01) relative risk of stroke.[20] Left atrial size was a weak factor in this study.

The annual risk of stroke was 3·6 % in the SPAF-III trial if a history of hypertension was present. Those who had hypertension (160 mmHg systolic) on enrolment had a risk of 12·4%. Patients aged 65–75 years with no risk factors had an annual risk of 1·1%. Patients older than 75 years without any risk factors had an annual risk of 3·5%. Patients aged 65–75 years with additional risk factors had an annual risk of 3·6%, while patients older than 75 years had an annual risk of 7·9%.

The CHADS2 Criteria was based on combination of two previous risk schemes (The Atrial Fibrillation Investigators, and Stroke Prevention in Atrial Fibrillation), and was subsequently validated as superior to either scheme.[21] The CHADS2 criteria gives 1 point each to congestive heart failure, hypertension, age greater than 75 years, and diabetes mellitus. Two points are given to people with history of an embolic event. Patients are considered low risk with a score of 0 (1·9% yearly risk of stroke), intermediate risk with a score of 1 or 2, and high risk with a score of more than 3 (18·2% yearly risk of stroke).

Summary

The prevalence of atrial fibrillation is increasing with our ageing population. The causative relationship with ischaemic stroke suggests a significant health burden to older individuals. This burden may be avoided with recognition and appropriate preventive medicine. Numerous large well conducted trials have been undertaken for various antithrombotic preparations. Warfarin is the most efficient, but is associated with limited bleeding tendencies. The risk can be reduced by appropriate management of INR, and selection of patients. In those unable to take warfarin, aspirin appears to be an appropriate alternative. The guidelines from the Royal College of Physicians do not recommend a dose for aspirin in atrial fibrillation and stroke prevention although The American Heart Association suggests 325 mg. CHAD2 scoring can be used to assess the risk of stroke in atrial fibrillation, and hence guide the physician.

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