

Warfarin and stroke prevention in AF

Stroke is a serious complication of atrial fibrillation, affecting not only the patient but people around them as well. It has a huge financial impact on the NHS. The use of warfarin reduces ischemic stroke but should not be taken lightly as the drug is associated with increased risk of haemorrhage. **Drs Anil K Agarwal, Ranjna Garg, S A Kauser and Stuart Hutchinson** look at the current status of warfarin use in the prevention of stroke in atrial fibrillation.

Cerebrovascular disease is the second most common cause of death worldwide. Ischaemic cerebrovascular disease is mainly embolic from cardiac source in patients with atrial fibrillation (AF)^{1,2}. Anticoagulation agents such as warfarin reduce the incidence of embolic stroke in these patients³⁻⁶. Non-valvular AF increases the risk of stroke, especially if patients have other co-morbid states (eg, congestive heart failure, hypertension or left ventricular dysfunction)⁷⁻⁸. Several strategies have been tried for the prevention of ischaemic stroke in patients with AF, with several trials recommending the use of anticoagulation or antiplatelet therapy⁹⁻¹¹. Warfarin is one anticoagulant that may be used. The benefits gained by reduction in embolic stroke may be offset by an increase in the incidence of haemorrhagic stroke^{12,13} or other warfarin-related complications (eg, gastrointestinal bleeding) that increase morbidity or mortality. Despite the benefits, anticoagulation should not be considered lightly due to the inherent risk involved.

Burden of stroke

The Department of Health's National Service Framework (NSF) for Older People shows that each year more than 110,000 people in England suffer from a stroke, costing over £2.8bn to the NHS in direct and indirect costs¹⁴. The implications of stroke for the patient and the family are huge in terms of lost earnings and the need for life-long care. The impact on the patient's quality of life, physical as well

as psychological, is important. Many of these patients have to move to care homes (10–20 per cent) and physical disability can also affect mental well-being. Patients suffering from stroke require help from a variety of healthcare providers — physiotherapists, continence nurses, district nurse support and other services. Thus, regular ongoing multidisciplinary team input is needed on a long-term basis making stroke prevention important.

AF and stroke prevention

AF is more prevalent in males than females. The risk of AF increases with age with highest incidence in the eighth decade¹⁴⁻¹⁷ — a six per cent prevalence among those older than 65 years and 25 per cent for those above 80 years¹. The yearly incidence of stroke with AF is about five per cent, five times higher than a patient in sinus rhythm¹.

Embolus in AF is a common causative factor in the pathogenesis of stroke, increasing risk by four- to fivefold in all age groups¹. There are other factors for stroke that may co-exist with AF¹⁸. Several therapeutic strategies for its prevention in AF have been attempted^{9,13,19}. Variable dose warfarin targeted to a international normalised ratio (INR) is more effective than aspirin or fixed low dose warfarin^{20,21}. Trials have looked at different anticoagulation approaches^{22,23}. Stroke prevention strategies have been formulated according to the underlying co-morbid status and risk factors. Anticoagulant

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therapy use is variable in clinical practice²⁴⁻²⁷. This is attributed to a number of factors such as variability in trial design, different dosage of the anticoagulants, and intensity of anticoagulation or populations studied. A large number of cross-sectional, population-based studies and clinical trials have looked at the issue of thrombotic stroke prevention in patients with AF. The risk/benefit ratio is important due to the increased risk of haemorrhagic stroke. Thus, trials have also looked at not only reducing the thrombotic stroke, but also at the optimal INR target that would balance out the risk of hemorrhagic stroke and bleeding²¹. Because of the huge impact on the NHS, it is important to have a consensus on the best prevention strategies. The National Institute for Health and Clinical Excellence (NICE) recommends such patients should receive thromboprophylaxis unless contraindicated²⁸. Warfarin should be used to keep INR between two and three. If warfarin is contraindicated, aspirin at 75–300mg daily should be used.

Warfarin and AF

The use of warfarin requires regular blood monitoring. Several randomised control studies have shown the benefits of anticoagulation in stroke prevention in non-valvular AF. There is still debate about effectiveness and safety of anticoagulation in clinical practice. The Stroke Prevention in Atrial Fibrillation II Study showed a reduction in the incidence of embolic stroke^{20,21}, but a higher rate of intracranial haemorrhage was also noted. This was attributed to higher INR chosen for the study. The absolute risk reduction in stroke was small.

In another open-labelled randomised controlled trial patients with AF and at least one thromboembolic risk factor were randomised to receive variable dose of warfarin (N=523) or fixed dose warfarin (to keep INR of 1.2 to 1.5 for initial dose adjustment) plus aspirin 325mg/day (N=521). Variable dose warfarin was adjusted according to the target INR two to three. Eligible patients (N=1044) were randomised and followed for the 2.5 years (mean). This study showed significant reduction in incidence of thromboembolic stroke in the variable dose warfarin group as compared to combination group (1.9 per cent vs 7.9 per cent per year) or absolute rate difference of six per cent per year with variable dose warfarin. Risk of major haemorrhagic events did not differ between both groups (2.4 per cent vs 2.1 per cent per year). Relative risk reduction of stroke/primary event in variable dose warfarin compared with combination therapy was 0.75. The

short duration of follow-up in this trial may not give exact replication in clinical practice as warfarin, once started, is given for life if there is no contraindication so complications may be underreported due to the short follow-up.

A systematic review of five major randomised controlled trials²⁹ on the primary prevention of stroke in adult patients with AF included BAATF (Boston Area Anticoagulation Trial for Atrial Fibrillation), SPAF-I (Stroke Prevention in Atrial Fibrillation Study), SPINAF (Stroke Prevention in Atrial Fibrillation trial), CAFA (Canadian Atrial Fibrillation Anticoagulation) and AFASAK-I (Atrial Fibrillation, Aspirin, Anticoagulation Trial) was performed. These studies included 2,313 participants with a mean age of 69 years. Four studies were placebo controlled trials against warfarin; in one study aspirin was evaluated against warfarin. Reported outcomes were all stroke, ischaemic stroke, haemorrhagic, fatal/disabling stroke and other vascular (thrombotic/haemorrhagic) events. The selected studies were properly designed/conducted trials with focused aims and objectives. The results showed that treatment with warfarin in patients with AF saved 25 strokes per year per 1,000 patients. The reduction in ischaemic stroke incidence was significant with warfarin vs control group.

Reduction in the incidence of other outcomes was similar to primary results in favour of warfarin (myocardial infarction, systemic arterial emboli, major extra cranial bleeding and vascular deaths). The reduction was similar for primary as well as secondary prevention. No significant increase in the incidence of intracranial bleed was seen. The interpretation and clinical applicability of these trials is important. It is difficult to apply the results in clinical practice for several reasons — different dosages used, differences in the targeted INR in different clinical trials, shorter duration of the follow-up and inclusion of younger patients. Most studies have shown variable outcomes.

Limitations of evidence

Stroke is predominantly a disease of elderly patients. The largest systematic review incorporating five randomised trials included younger patients than usual²⁹. This cannot be equated to the general clinical practice. The duration of follow-up was short — warfarin is used for life. Due to the selection criteria, mainly fit younger patients were included in the trial. The effect of polypharmacy and drug

interactions on INR, and the effect of other drugs on incidence are not clear from the studies, though the systematic review does briefly address the risk stratification; it would be useful to see the results adjusted for individual risk factors. In addition, patients had more than standard care and it is not clear from either study whether other risk factors for stroke, such as hypertension and dyslipidemia, were managed. It would also be interesting to see if the effect of anticoagulation was over and above the benefits of tight blood pressure and lipid control. Target INR was easy to manage in the context of trial setting with frequent input by the investigators. This is not practical, often not possible and patients have high incidence of high/low INR. This may skew the data in real world. Thus, a trial selectively on AF with no other risk factors in patients >75 years age, might give valuable information.

Warfarin and haemorrhage

Use of anticoagulation therapy increases the risk of bleeding³⁰. This risk can be reduced by low intensity warfarin use by keeping INR between two and three³¹. At this level of INR, risk of thrombotic and haemorrhagic stroke are balanced. An observational study showed the risk of intracranial haemorrhage is increased in patients aged >80 years³⁰. Hylek *et al*, showed that many elderly patients were not candidates for anticoagulation, though at the high risk of stroke. This is due to several factors, such as risk of fall or polypharmacy³². This may be attributed to the co-morbidities. That this group of patients need close monitoring — as does anticoagulation therapy — may be one reason variable dose warfarin therapy has been studied³³⁻³⁶ or a combination of low dose warfarin plus aspirin. These studies are less effective in stroke prevention than INR-targeted warfarin therapy.

Variability in the use of warfarin in stroke prevention was highlighted in the ATRIA study³⁷. No reason for the variability in warfarin prescribing could be found in it. Under-utilisation of anticoagulation in older patients may be due to variable trial designs with small number of patients¹⁶⁻¹⁸. This may also be due to the physician's inability to interpret the data in the context of the trial. A trial conducted in hospitalised patients may have older patients with multiple risk factors. The inability to apply this data to ambulatory patients in general practice has led to more trials in those patients³⁷ involving a large at risk population. This large cohort study showed the use of warfarin caused reduction in all cause mortality. Though the risk of intracranial haemorrhage was

higher in patients taking warfarin, it was not associated with increased adjusted risk of non-intracranial haemorrhage.

Intracranial haemorrhage (ICH) is an important complication because it produces neurological deficit and death nullifies the benefit achieved by warfarin³⁰. The higher rate of ICH was observed in the SPAF II study — 1.8 per cent in those using warfarin compared with 0.8 per cent in those receiving aspirin²⁰. This was attributed to the use of a higher INR target whereas the risk of haemorrhage was 0.3 per cent per year in other prevention trials³⁸⁻³⁹. While ICH is an important side effect, incidence of ICH is small, increasing when the target value of INR is >4.0. A meta-analysis showed there is a 46 per cent reduction of ischaemic stroke with an adjusted dose of warfarin compared with aspirin³⁴. In the AFASAK and EAFT trial, adjusted dose warfarin decreased the relative risk of ischemic stroke by 48 per cent and 40 per cent respectively as opposed to aspirin⁴¹⁻⁴². Many patients with AF understand the consequences of stroke and choose warfarin even for a relatively small decrease in absolute risk of stroke. Other patients may not opt to use warfarin as its use imposes certain lifestyle modifications regarding alcohol use and frequent monitoring of anticoagulation intensity. They may also fear the risk of ICH/bleeding. In addition to clinical risk stratification, patient's wishes should be given due consideration and they should be allowed to make an independent decision.

Summary

Despite so much research, there are areas that need further clarification. AF patients aged 75 years or more are at increased risk of embolic stroke. They may also be at high risk of bleeding or falls. There is a need for long-term studies in the people aged >75 years. The risk/benefit in this group of patients needs more clarification and there is a need for concise guidelines.

The use of warfarin in stroke prevention has been subject to notable differences in trial designs — for instance, age of the participants, duration of the trial, placebo controlled or aspirin controlled, presence of risk factors and co-morbid states. Initiation of warfarin should take into consideration a risk/benefit assessment. Risks should be carefully weighted against the potential benefits of stroke prevention. Careful patient selection should avoid these pitfalls. The presence of other risk factors should be addressed and treated. Stroke prevention

in patients with AF is best achieved with use of warfarin. There is an inherent risk of bleeding, but this can be minimised by appropriate close monitoring of INR. The use of subtherapeutic INR targets using low dose warfarin with or without aspirin has inconsistent results. The suggested INR range is from two to three. At this INR range, risk of hemorrhagic stroke is more often offset by the benefits achieved. Appropriate stroke prevention strategies would reduce the related mortality and disability, and have major cost impact on NHS and patients' well being.

Conflict of interest: none declared.

Key points

- Atrial fibrillation increases the risk of stroke in all age groups.
- The benefits of warfarin in stroke prevention have been shown in randomised control trials.
- A careful risk/benefit assessment should be done when considering warfarin for stroke prevention.
- Risk/benefits should be explained to the patients so that they can take well-informed decision.

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