

Nonvalvular Atrial Fibrillation and Stroke: A Review

Pages with reference to book, From 242 To 245

Shahid Anis Khan (Department of Cardiology, West Middlesex University Hospital, Isleworth, U.K.)

Abstract

Nonvalvular atrial fibrillation accounts for more than thirty percent of all strokes above the age of sixty years. The use of anticoagulants for the primary prevention of stroke has been a controversial issue for a long time. New data has emerged which clarifies some of these issues and helps in selecting patients who are at a higher risk of stroke (JPM 43:242,1993).

There are many cardiac pathologies which can predispose towards thromboembolism and cerebrovascular accidents¹. However, nonvalvular atrial fibrillation is one of the commonest preventable causes of ischemic stroke. Atrial fibrillation not associated with valvular heart disease is a common arrhythmia. It affects 2 to 5% of the population above the age of 60 years² and there is a fold increase in the risk of stroke in those with atrial fibrillation. It accounts for up to one third of all strokes above the age of 60 and this risk increases with age^{3,4}. There is a general agreement that patients with valvular heart disease and atrial fibrillation should be anticoagulated with warfarin to prevent thromboembolic complications and strokes^{5,6}. Although systemic embolisation and cerebrovascular accidents are lethal complications of nonvalvular atrial fibrillation^{4,7}, considerable controversy exists over the use of anticoagulants for their prevention^{8,9}. The concept of anticoagulation in chronic atrial fibrillation is not new¹⁰. Although anticoagulation for the prevention of thrombotic problems seems a rational approach^{11,12}, doubts exist over the preventative role and long term safety especially in elderly patients¹³. The use of antithrombotic treatment for prophylaxis has been further complicated as the required dose or the degree of anticoagulation is not clear. Uncertainty also exists over the duration of treatment and the selection of high risk groups. Recently new data has emerged regarding stroke prevention in nonvalvular atrial fibrillation. Five prospective trials of stroke prevention in nonvalvular atrial fibrillation have terminated early. The results of these trials help clarify some of the questions surrounding routine prophylactic use of antithrombotic agents in nonvalvular atrial fibrillation. In the Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study (AFASAK)¹⁴, 1007 out-patients with chronic non-rheumatic atrial fibrillation were studied. In this placebo-controlled, randomised trial, 335 patients (median age 72.8 years) received warfarin (maintaining international normalised ratio (INR) of 2.4-4.2), 336 patients (median age 75.1 years) received aspirin 75 mg daily and 336 (median age 74.6 years) a placebo. The patients were followed up for 2 years. The end point was thromboembolism or death. The yearly incidence of thromboembolic complications was 2.0% (95% confidence limit 0.6%, 4.8%) with warfarin and 5.5% (95% confidence limit 2.9%, 9.4%) with aspirin and placebo. The incidence of side effects in the warfarin group was 7%. In the warfarin group 4 patients had cerebral infarct and only 1 patient had haemorrhagic stroke. Of the 4 embolic strokes only one occurred during sufficient anticoagulation. 23 patients (7%) were withdrawn from the study due to the side effects of warfarin. In aspirin group only 2 episodes of bleeding were noted. In this study there were 3 vascular deaths in the warfarin group, 12 in the aspirin group and 15 in the placebo group. The incidence of thrombotic complications and mortality was significantly lower in the warfarin group. There was no significant difference between the aspirin and the placebo group. Thus prophylactic therapy was recommended to prevent thromboembolism in patients with nonvalvular atrial fibrillation. In the

randomised, placebo controlled trial of Stroke Prevention in Atrial Fibrillation (SPAF) ¹⁵, 1330 patients were followed for a mean period of 1.13 years. Patients were randomised to two groups and those eligible (most less than 76 years) were given warfarin (INR maintained between 2-4.5), aspirin (325 mg once daily) or placebo (group I). Those who were not eligible for warfarin were assigned to group II and were either given aspirin (325 mg) or a placebo. The mean age of the patients was 67 years and the end point was systemic embolism or stroke. Risk reduction of primary event in the warfarin group was 67%. Primary event or death were reduced to 58% by warfarin ($P=0.01$) and 32% by aspirin ($P=0.02$). The risk of significant bleeding was 1.5% in the warfarin group, 1.4% in the aspirin group and 1.6% in the patients assigned to the placebo. In the warfarin group there was one fatal intracerebral haemorrhage and one subdural hematoma with full recovery. In the aspirin group there was one fatal subdural hematoma. In the placebo group there were 2 subdural hematomas with full recovery. The compliance was 87.7% in the warfarin group and 88% in the aspirin group. The data from this study indicated that prophylactic therapy with warfarin or aspirin was effective in the short term in patients with nonvalvular atrial fibrillation. However, there was no benefit with aspirin in patients above 75 years of age. The trial is continuing in order to address the question of the relative efficacy of aspirin and warfarin. Therefore the data on events is not reported separately for these drugs. In the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) ¹⁶ the efficacy of low dose warfarin on the risk of stroke in nonvalvular atrial fibrillation was assessed. In this trial 420 patients with a mean age of 68.5 years (8.5 years) were followed up for an average period of 2.2 years. Patients were randomised to warfarin (INR 1.5-2.7) or the control group. In this group 39% of patients were above 70 years and 8% above 80 years of age. Aspirin (325 mg once daily) was allowed in the control group and was taken by 46% of the patients. There were 2 strokes in the warfarin group in 487 years of patient observation (incidence 0.41% per year) as compared to 13 strokes in the control group in 435 years of patient observation (incidence of 2.98% per year). 46% of all the patient years in the control group were contributed by patients taking aspirin. Eight of the 13 strokes occurred among patients taking aspirin, an incidence of 3.99% per year for strokes. There was an 86% reduction in the risk of stroke in the warfarin group. The overall death rate was lower in the warfarin group (11 deaths) than the control group (26 deaths). The major bleeding events leading to hospital admission or transfusion were essentially similar, i.e., 2 in the warfarin and one in the control group. There were no cerebral haemorrhages recorded in the patients who had stroke. It was concluded that with careful monitoring, long term low dose warfarin (INR 1.5-2.7) was highly effective in preventing strokes in patients with nonvalvular atrial fibrillation. The result of all recent trials have reported that moderate anticoagulation to achieve an INR between 1.5-3 reduces the risk of first time stroke by about two thirds. The similarity in the results of these recent studies is quite remarkable ¹⁴⁻¹⁸. The evidence provided puts forward a strong case for the prophylactic use of warfarin in patients with nonvalvular atrial fibrillation. The use of low dose warfarin seems promising as there were few side effects along with adequate protection against strokes with good drug compliance. It is evident that not all patients with nonvalvular atrial fibrillation develop thromboembolism. The logistical problem of anticoagulating a large number of patients as well as monitoring them over a period of years can stretch resources. Hence identification of high risk and low risk groups is of paramount importance.

High Risk Groups

In the BAATAF study ¹⁶, patients with intermittent atrial fibrillation were compared with a group of patients with sustained atrial fibrillation. The risk of stroke was similar in both groups. However, in the FASAK ¹⁴ trial it was noted that the frequency of thromboembolism increased with the duration of atrial fibrillation. Other studies have also suggested that constant atrial fibrillation had a greater association with strokes than transient atrial fibrillation ¹⁹⁻²¹. Hence contrary to widely held belief, patients with chronic atrial fibrillation are at a higher risk of stroke as compared to patients with paroxysmal atrial fibrillation. Nonetheless there is tendency of transition from intermittent atrial

fibrillation to sustained atrial fibrillation. Recently new data has emerged which helps select those at high risk of arterial thrombosis^{22,23}. The analysis of 568 patients with nonvalvular atrial fibrillation assigned to the placebo group in a randomised clinical trial were studied for a mean period of 1.3 years²². Clinical variables were assessed and correlated with systemic embolism and stroke. The results of the study showed that the history of recent congestive cardiac failure (within 3 months), hypertension and previous history of thromboembolism were independent risk factors for thrombotic complications (>7% per year; $P < 0.05$). Patients without the above mentioned clinical risk factors accounted for 42% of the group and had only a 2.5% risk of thrombotic events per year. The patients with one risk factor had an event rate of 7.2% per year and for those with two or three risk factors, the event rate was 17.6% per year. The subjects under 60 years of age without any risk factors had no thromboembolic complications. The use of echocardiography can be of great value in selecting patients at high risk. It has been shown that left ventricular hypertrophy, left ventricular dysfunction and increased left atrial diameter are strong independent risk factors for subsequent thromboembolic events in patients with nonvalvular atrial fibrillation²³⁻²⁶.

Low Risk Group

It has been noted that patients with “lone atrial fibrillation”, i.e., atrial fibrillation in the absence of other clinical heart disease, have a lower risk of stroke¹⁶. In the SPAF¹⁵ study out of 51 patients with lone atrial fibrillation there was no recorded episode of stroke or thrombosis. In another study, 3623 patients under 60 years of age with atrial fibrillation were studied¹⁹. The incidence of lone atrial fibrillation was 2.7%. In this group of patients with lone atrial fibrillation there were few episodes of stroke. The risk of thromboembolism was 0.55% per year and hence routine anticoagulation was not recommended. Though lone atrial fibrillation carries a low risk of stroke in younger patients, its benign nature still needs evaluation in elderly patients with nonvalvular atrial fibrillation.

The Elderly

Nonvalvular atrial fibrillation is a common arrhythmia in the elderly²¹. It accounts for 7-31% of all strokes above the age of 60 years and this risk of stroke increases with age³. On the other hand the incidence of cerebral haemorrhage also increases with increasing age²⁷. The risk of cerebral haemorrhage during anticoagulant treatment is about ten times higher than in patients not on anticoagulants and this effect is independent of age. Hence for patients above the age of 80 years the risk of cerebral haemorrhage would be considerable and should be weighed against any significant benefit from prolonged anticoagulation. In the elderly, other factors like falls, drug interactions, polypharmacy and social isolation need consideration. The dose of warfarin required to achieve the desired therapeutic benefit decreases with age²⁸. This age-associated increased sensitivity to warfarin, can pose further problems for the prescribing physician^{29,30}. However, age by itself should not be considered a contraindication for long term anticoagulation. In a study of elderly patients aged 65 to 89 years on anticoagulants, 49 subjects were followed over a mean period of 3.9 years³¹. The only factor associated with poor anticoagulation was the concomitant use of drugs known to affect warfarin metabolism. The treatment failure rate was 4% but was not related to age. This study which was exclusively in the elderly (mean age 72.9 years) showed a low rate of major haemorrhage and no deaths due to anticoagulation therapy.

Cost

One of the major considerations regarding any therapy is the cost effectiveness. Gustafsson and colleagues assessed the potential effects of primary prevention with anticoagulants or aspirin in atrial fibrillation on the Swedish population³². The direct and indirect cost of stroke saved, number of stroke prevented and cost of preventive treatment was calculated. The authors calculated that when the rate of intracranial bleeding exceeded 2% per patient year of warfarin therapy then the anticoagulation is not cost effective. However, the treatment is cost effective provided the risk of haemorrhagic complications

are kept low as seen in carefully selected patients in the previous trials¹⁴⁻¹⁸.

Conclusion

In view of the accumulated evidence it seems reasonable to recommend prophylactic therapy in all patients with nonvalvular atrial fibrillation provided there are no specific contraindications. At present warfarin seems the drug of choice (maintaining INR between 1.5-3) and the role of aspirin as a preventative drug is debatable especially in patients above 60 years of age. Patients with chronic atrial fibrillation, congestive cardiac failure, hypertension and those with a previous history of thromboembolism are at a higher risk of thrombotic complications and stroke. Thus as a high risk group they need serious consideration for prolonged anticoagulation. The use of echocardiography can be of great help to the physician in the selection of high risk patients. Large scale studies are required to identify further sub-groups of patients, with non valvular atrial fibrillation who are at a higher risk of embolic complications. Work is needed in the very elderly age group, i.e. patients above the age of 80 years. Research is also needed in searching for a more convenient and safer prophylactic therapy, with fewer side effects. The long term success of anticoagulation with non valvular atrial fibrillation will depend upon careful patient selection and close monitoring.

References

1. Hart, R.G. Cardiogenic embolism to the brain. *Lancet*, 1992;339:589-94.
2. Peterson, P. and Godtfredsen, S. Atrial fibrillation - a review of causes and progress. *Acta. Med. Scand.*, 1984;216:5-9.
3. Wolf, P.A., Dawber, T.R., Thomas, H.E. Jr. et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: Framingham study. *Neurology*, 1978;28:973-77.
4. Wolf, P.A., Abbott, R.D. and Kannell, W.B. Atrial fibrillation as an independent risk factor for stroke: The Framingham study. *Stroke*, 1991;22:983-88.
5. Szekely, P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *Br. Med. J.*, 1964;1:1209-12.
6. Anonymous. Anticoagulants in mitral valve disease (Editorial). *Br. Med. J.*, 1972;1:64.
7. Hinton, R.C., Kistler, J.P., Fallon, J.T. et al. Influence of etiology of atrial fibrillation on incidence of systemic embolism. *Am. J. Cardiol.*, 1977;40:509-13.
8. Seizer, A. Atrial fibrillation revisited. *N. Engl. J. Med.*, 1982;306:1044-45.
9. Dunn, M., Alexander, J., D'Silva, R. and Hilder, F. Antithrombotic therapy in atrial fibrillation. *Chest*, 1989;95:118S-127S.
10. Fisher, C.M. Treatment of chronic atrial fibrillation. *Lancet*, 1972;1:1284.
11. Stein, B., Fuster, V., Halperin, J.L. et al. Antithrombotic therapy in cardiac disease. *Circulation*, 1989;80:1501-13.
12. Roy, D., Marchand, B., Gage, P. et al. Usefulness of anticoagulation therapy in prevention of embolic complications of atrial fibrillation. *Am. Heart J.*, 1986;112:1039-43.
13. Kutner, M., Nixon, G. and Silverstone, F. Physicians' attitudes towards oral anticoagulation and antiplatelet agents for stroke prevention in elderly patients with atrial fibrillation. *Arch. Intern. Med.*, 1991;151:1950-53.
14. Peterson, P., Boysen, G., Godtfredsen, S. et al. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: The Copenhagen AFASAK study. *Lancet*, 1989;1:175-78.
15. Stroke prevention in atrial fibrillation investigators. Stroke prevention in atrial fibrillation study final results. *Circulation*, 1991;84:527-39.

16. The Boston area anticoagulation trial for atrial fibrillation investigators. The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. *N.Engl.J.Med.*, 1990;323:1505-11.
17. Connolly, S.J., Laupacis, A., Gent, M. et al. Canadian atrial fibrillation anticoagulation (CAFA) study. *J.Am.Coll. Cardiol.*, 1991;18:349-55.
18. Ezekowitz, M.D., Bridgers, S.L., James, K.E. et al. Warfarin in the prevention of stroke associated with non-rheumatic atrial fibrillation. *N.Engl.J.Med.*, 1992;327:1406-12.
19. Kopecky, S.L., Gersh, B.J., McOoon, M.D. et al. The natural history of lone atrial fibrillation. *N. Engl.J. Med.*, 1987;317:669-74.
20. Peterson, P. and Godtfredsen, S. Embolic complication in paroxysmal atrial fibrillation. *Stroke*. 1986;17:622-26.
21. Treseder, A.S., Sastry, B., Thomas, T.P.L et al. Atrial fibrillation and stroke in elderly hospitalized patients. *Age, Ageing*. 1986;15:89-92.
22. The stroke prevention in atrial fibrillation investigators. Predictors of thromboembolism in atrial fibrillation I. Clinical features of patients at risk. *Ann. Intern. Med.*, 1992;116:1-5.
23. The stroke prevention in atrial fibrillation investigators. Predictors of thromboembolism in atrial fibrillation II. Echocardiographic features of patients at risk. *Ann.Intern.Med.*, 1992;116:6-12.
24. Ruocco, N.A. and Most, A.S. Clinical and echocardiographic risk factors for systemic embolisation in patients with atrial fibrillation in the absence of mitral stenosis. *J.Am.Coll. Cardiol.*, 1986;7:165.
25. Arrow, W.S., Outstein, H. and Haiech, F.Y. Risk factors for thromboembolic stroke in elderly patients with chronic atrial fibrillation. *Am.J. Cardiol.*, 1989;63:366-67.
26. Lewy, D., Plehn, J.F., Wolf, P.A. et al. Left ventricular mass and risk of stroke in men. *Circulation*, 1987;76(suppl IV):143.
27. Wintzen, A.R., de Jong, H., Loeliger, E.A. et al. The risk of intracerebral hemorrhage during oral anticoagulant treatment: a population study. *Ann. Neurol.*, 1984;16:553-58.
28. Redwood, M., Taylor, C., Sam, B.J., et al. The association of age with dosage requirement for warfarin. *Age Ageing*, 1991;20:217-20.
29. O'Malley, K., Stevenson, I.H., Wood, A.J.J. et al. Determination of anticoagulant control in patients receiving warfarin. *Br.J.Clin.Pharmacol.*, 1990;4:309-14.
30. Shepherd, A.M.M., Hewick, D.S., Moreland, T.A. et al. Age as a determinant of sensitivity to warfarin. *Br.J.Clin. Pharmacol.* 1977;4:315-20.
31. Wickramasinghe, L.S.P., Basu, S.K. and Bansal, S.K. Longterm anticoagulation therapy in elderly patients. *Age Ageing*, 1988;17:388-96.
32. Gustafsson, C., Asplund, K., Britton, M. et al. Cost- effectiveness of primary stroke prevention in atrial fibrillation.: Swedish national perspective. *Br.Med.J.*, 1992;305:1457-60.