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Antithrombotic treatment and atrial fibrillation

Warfarin reduces the risk of first time strokes by two thirds

Non-rheumatic atrial fibrillation increases the risk of stroke by a factor of five and is present in about 15% of patients with acute stroke.[1,2] Its prevalence in the general population increases with age—from 0·5% at 50-59 to 8·8% at 80-89.[2]

The risk of someone with atrial fibrillation having a stroke is about 5% a year and increases with age, blood pressure, and other evidence of heart disease. In addition, atrial fibrillation is associated with a greater early mortality in patients admitted to hospital with acute stroke[3] and a greater risk of recurrent stroke,[4] although these associations were not found in the Framingham community study.[5] Two articles in this week's journal are relevant to the use of antithrombotic treatment in people with atrial fibrillation—whether as primary prevention, acute treatment, or secondary prevention of ischaemic stroke (pp 1457,[6] 1460[7]).

Five randomised controlled trials have reported on the use of warfarin in the primary prevention of stroke in people with non-rheumatic atrial fibrillation.[8-12] Their results consistently show that moderate anticoagulation (to achieve an international normalised ratio between 1·5 and 3·0) reduces the risk of stroke by about two thirds. The efficacy of warfarin may be even greater because many strokes in the groups treated with warfarin occurred when the patients were not taking the drug.[13] A prospective meta-analysis of such trials is currently in progress.[14] The impressive efficacy of warfarin in preventing stroke suggests that anticoagulation may prevent not only cerebral infarctions caused by emboli from the heart but also infarctions due to emboli from atheromatous plaques in the aortic arch and the carotid and vertebral arteries.

Prophylaxis with warfarin has two main problems: hassle and safety. Patients need regular education, and the effect of warfarin must be monitored and the dose adjusted. Anticoagulants increase the risk of major bleeding, particularly gastrointestinal, retroperitoneal, and intracranial bleeding. Intracranial bleeding may cause strokes with higher morbidity and mortality than the thromboembolic strokes that warfarin prevents. Compliance and safety are likely to be less assured when warfarin is prescribed in general practice than in the carefully selected, well motivated, and tightly monitored participants in trials of warfarin.[8-13] For prophylaxis with warfarin the ratio of antithrombotic benefit to risk of bleeding will depend critically on the selection of patients and the quality of their medical and haematological monitoring.

In this week's journal Gustafsson and colleagues have calculated the cost effectiveness of primary prophylaxis with anticoagulants, using Swedish data (p 1457).[6] The authors assume that 26% of people with atrial fibrillation are potential candidates for warfarin, which reduces their annual risk of stroke from 5% to 1·8%. They calculate that when the rate of intracranial bleeding during prophylaxis is only 0·3% per patient year (as in the published trials[8-12]) warfarin reduces the numbers and costs of stroke. But when the rate of intracranial bleeding rises to 2% per patient year warfarin is no longer cost effective.

The message for doctors considering primary prophylaxis with warfarin in people with atrial fibrillation is therefore clear: if you wish to do more good than harm choose patients at sufficiently high thromboembolic risk (defined by age; history of hypertension, ischaemic heart disease, or heart failure; and left atrial size and left ventricular dysfunction at echocardiography); exclude patients with contraindications to long term anticoagulation (poor compliance, bleeding disorders, potential bleeding lesions); review your patients, their anticoagulant control, and the performance of your local anticoagulant clinic regularly; and ensure rapid access to hospitals with adequate diagnostic and therapeutic services in the event of suspected potentially disabling or fatal intracranial, gastrointestinal, or retroperitoneal bleeding.[15]

Doctors reluctant to prescribe warfarin often prescribe aspirin, which carries less need for monitoring and less risk of bleeding. Only two of the five trials of warfarin in people with atrial fibrillation have also reported the reduction of risk in patients treated with aspirin[8,10]: aspirin seems to reduce the risk of stroke by about 25%. The 95% confidence intervals, however, include zero benefit, so that further trials are required before aspirin can be confidently recommended for primary prevention.[13] The potential cost-benefits of prophylaxis with aspirin as estimated by Gustafsson *et al* similarly require caution.[6]

What is the therapeutic relevance of atrial fibrillation in patients with acute stroke? In this issue (p 1460) Sandercock and colleagues report that in the Oxfordshire community stroke project the 17% of patients with acute stroke and atrial fibrillation had a significantly higher 30 day mortality than patients in sinus rhythm (23% versus 8%).[7] Similarly, a study of patients admitted for acute severe stroke found that the 25% with atrial fibrillation had a significantly higher hospital mortality than patients in sinus rhythm (67% versus 44%).[3] This higher early mortality is partly explained by the association of atrial fibrillation with large, total anterior circulation

infarcts presumably due to occlusion of the main stem of the middle cerebral artery.[7] It is tempting to speculate that many of these occlusions are due to large fibrin rich emboli from atrial thrombi[15] and that prompt treatment with thrombolytic drugs or at least aspirin or heparin might reduce the early mortality in patients with atrial fibrillation by minimising thrombotic extension or recurrence of thromboemboli.

The roles of all three antithrombotic regimens in acute ischaemic stroke remain to be established by current large international trials.[16] In the subgroup analyses of these trials it will be interesting to see whether patients with atrial fibrillation have a higher ratio of benefit to risk than patients in sinus rhythm. Sandercock *et al* also show that atrial fibrillation is almost as common in patients with intracerebral haemorrhage (11%) as in patients with cerebral infarction (18%), making computed tomography of the brain to exclude intracranial bleeding mandatory before any antithrombotic treatment is started,[16] irrespective of heart rhythm.

Finally, what is the therapeutic relevance of atrial fibrillation in survivors of a first stroke? Sandercock and colleagues show that between 30 days and six years survivors of stroke with atrial fibrillation have a risk of recurrent stroke or vascular death similar to that of those in sinus rhythm.[7] Both groups of patients therefore require secondary preventive measures, including antithrombotic treatment: aspirin in a dose of 75-300 mg daily is currently the recommended regimen.[16] Studies are currently underway comparing anticoagulants with antiplatelet drugs in the secondary prevention of cardiovascular events in patients with previous ischaemic stroke or transient cerebral ischaemic attacks. Results in patients with atrial fibrillation (included in the European atrial fibrillation trial) will be reported next year.[16]

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Stroke rehabilitation: can we do better?

Emphasising physical recovery may be counterproductive

Stroke may have severe and long lasting physical, emotional, and social consequences for patients and their families. Although there is a consensus that patients who have had a stroke benefit from multidisciplinary rehabilitation, there is less agreement about how this should be organised and what it should comprise. Nearly all patients who survive a stroke experience some spontaneous recovery, with about four in five being able to walk independently within six to 12 months.[1] Most recovery occurs within the first few months,[2,3] which is when patients receive the most intensive rehabilitation.

Developments in physiotherapy have emphasised the importance of intrinsic recovery and facilitating normal movement and tone in treating stroke.[4] This approach now forms the basis of accepted practice in Britain despite the lack of evidence that it works. Moreover, its dominance has meant that the expectations of the patient, family, and staff focus mainly on physical recovery. By default, physical recovery has become the most important outcome measure of stroke rehabilitation, dictating, for example, the timing of discharge from hospital, the provision of community services, and the need for respite care.

This emphasis on the recovery of physical function has arguably led to increasing neglect of the emotional and social consequences of stroke. Wade has emphasised that rehabilitation should aim to include helping the patient adapt as well as possible to the difference between his or her desired and achieved role.[5] Evidence suggests that, despite the large amount of money spent on caring for patients with stroke (about 4% of the NHS budget[6]) and the widespread introduction of multidisciplinary rehabilitation, this objective is not being achieved.[7,8]

Many patients, even some with good physical recovery, are socially inactive and have high levels of psychological morbidity. The range of possible emotional disorders is wide and includes anxiety, agoraphobia, and pathological emotionalism.[9] Depressive symptoms are more than twice as common as in age matched controls.[10] Much of this psychological morbidity, however, remains apparently undetected or ignored: few patients who have had a stroke receive antidepressants.[11] Many studies have highlighted the social inactivity of patients. One study found that 90% of patients were able to walk indoors and climb stairs independently, but many of them were effectively housebound.[1]

The patient's family is important in rehabilitation, but the psychological burden is heavy. Many carers suffer from frustration, stress, and frank depression, which increase with time and become progressively unrelated to the patient's physical ability.[12,13]

Several reasons may be suggested for the generally poor longer term outcome for patients who have had a stroke and their carers. Poor liaison between hospital and community services or poor coordination of community services may result in fragmented delivery of services. If the patient