THE BOTTOM LINE
The bottom line for neurologists is that atrial fibrillation (AF) patients who have had an ischaemic stroke or transient ischaemic attack (TIA) are at high risk of recurrent stroke and should be treated long-term with adjusted-dose warfarin (target INR = 2.5) for secondary prevention, provided it can be given safely and the blood pressure well controlled. For acute management, give aspirin until therapeutic anticoagulation is achieved. Please glance quickly at the attractive figures and illuminating tables, and then skip to the next article unless you want more detail!

SOME HISTORY
By the early 1980s, it was clear from cohort, case-control and autopsy studies that non-valvular AF (i.e. not associated with mitral valvular disease) was a strong, independent risk factor for ischaemic stroke. Based on the presumed pathogenesis of thrombus forming in relatively static blood in the left atrial appendage and then embolizing to the brain (Fig. 1), it seemed likely that antithrombotic drugs would reduce the risk of stroke. But concern about whether elderly AF patients could tolerate such treatments without excessive bleeding, particularly in the brain, meant that randomized controlled trials had to be performed to define the overall balance of benefit and risk. However, leading American cardiologists at the time assured us that such trials would be 'a waste of time' and even prominent European neurologists were not enthusiastic, doubting whether a trial of warfarin for secondary prevention was even feasible (Sandercock et al. 1986; Lodder et al. 1988). So we had to vigorously defend testing warfarin...
anticoagulation in elderly patients, even in a clinical trial setting, because in that era of high-intensity anticoagulation, which in the US was monitored with unreliable prothrombin time ratios, anticoagulation was generally thought to be contraindicated for anyone over the age of 75. This experience confirms the dubious value of expert opinion and non-randomized treatment comparisons, even (and perhaps especially) when offered by persuasive purported authorities.

By ignoring this ‘sage’ advice of the experts, what is known about stroke prevention for AF patients has advanced a very long way in the last couple of decades. In May 1985 the first patient was entered into the Stroke Prevention in Atrial Fibrillation (SPAF) trials and randomly assigned to receive aspirin – later in the trial he died of a myocardial infarction. Since then, a score of randomized controlled trials carried out by investigators throughout the world have solidly established the value of antithrombotic agents for stroke prevention in AF (Hart et al. 1999a; Hart et al. 2003b). While both restoration of sinus rhythm and mechanical obliteration of the stasis-prone, thrombogenic left atrial appendage are being explored by cardiologists for stroke prevention, antithrombotic agents will remain the mainstay of management for the foreseeable future.

EFFICACY OF ANTITHROMBOTIC TREATMENTS

Two types of antithrombotic treatment are firmly established for reducing stroke in AF patients: adjusted-dose warfarin (tested with INRs from...
Neurologists generally become involved with AF patients after a stroke or TIA has occurred (although we should spread the word about primary prevention of stroke in AF to our primary care colleagues). Secondary prevention is relatively straightforward: adjusted-dose warfarin (target INR 2.5) if at all possible. AF patients with a TIA or an ischaemic stroke are at high risk for stroke, averaging 10% per year if given just aspirin. In the recent pooled analysis, the relative risk reduction was 60% by warfarin over aspirin for the 986 patients with prior stroke or TIA and, more importantly, the absolute risk reduction was an impressive 6% per year (Table 2). This benefit was offset partially by an increased risk of major haemorrhage of 1.5% per year. In short, for secondary prevention of stroke in AF patients, the risk of recurrent stroke is intolerably high despite aspirin, and the benefits of adjusted-dose warfarin are large and generally not offset by the risk of major haemorrhage. In fact, the impressive overall benefit often cited for warfarin over aspirin in patients with atrial fibrillation is largely driven by the treatment of those with prior cerebral ischaemia rather than in primary prevention. In the pooled analysis, the numbers-needed-to-treat with warfarin for 1 year to prevent one stroke was 43 overall for unselected AF patients, but 17 for secondary prevention and 83 for primary prevention (Table 2).

Should TIA patients be managed any differently than ischaemic stroke patients? While AF is a strong, independent risk factor for ischaemic stroke, it is only weakly associated with TIA (Anderson et al. 2002; Harrison 1.6 to 3.0) reduces the relative risk of stroke by about 60%, and aspirin reduces it by about 20% (reducing mainly the smaller, non-cardioembolic strokes that occur in elderly AF patients) (Table 1). Our recent pooled analysis of 4052 patients from six randomized controlled trials showed a 45% (95% confidence interval (CI) 29 to 57%; P < 0.0001) relative risk reduction in all stroke by adjusted-dose warfarin vs. aspirin (van Walraven et al. 2002) and should supersede a preceding misleading meta-analysis (Taylor et al. 2001). The value of other antithrombotic agents and regimens is presently unclear.

So should it be ‘warfarin all around’ for AF patients? Certainly not! Many AF patients, including most patients who are under the age of 75, do not benefit sufficiently from anticoagulation to justify its use over aspirin for primary prevention. Adjusted-dose warfarin should be urged for the one-third of AF patients at high risk for stroke, and aspirin for the third at low risk. For the remaining third at moderate risk, talk about it with the patient and consider the individual patient’s bleeding risk, access to good-quality anticoagulation monitoring, and their preferences. This is analogous to carotid endarterectomy: surgery reduces the risk of stroke for many patients with moderate-to-severe carotid stenosis, but its optimal application is contingent on stratifying the individual patient’s risk, influenced importantly by the presence of recent symptoms and the degree of stenosis. Similar stroke risk stratification schemes have been developed and validated for AF patients (Hart et al. 2003a; Gage et al. 2003) and estimation of the inherent risk in the individual patient (which varies more than 20-fold) should be the first step in decisions concerning antithrombotic prophylaxis.

Table 1 Efficacy of antithrombotic drugs for stroke prevention in atrial fibrillation: meta-analysis of the randomized trials* adapted from Hart et al. (1999a)

<table>
<thead>
<tr>
<th>Drug Comparison</th>
<th>Number of Trials</th>
<th>Number of Patients</th>
<th>Relative Risk Reduction (95% CI)</th>
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<tbody>
<tr>
<td>Adjusted-dose warfarin vs. control†</td>
<td>6</td>
<td>2900</td>
<td>62% (48 to 72)</td>
</tr>
<tr>
<td>Aspirin vs. placebo</td>
<td>6</td>
<td>3119</td>
<td>22% (2 to 38)</td>
</tr>
<tr>
<td>Antiplatelet vs. placebo‡</td>
<td>6</td>
<td>3337</td>
<td>24% (7 to 39)</td>
</tr>
</tbody>
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*Stroke includes both ischaemic and haemorrhagic.
†Three trials were placebo controlled.
‡Includes 218 patients given dipyridamole alone or combined with aspirin.
Most strokes in AF patients are due to embolism of left atrial appendage thrombi, but an important minority are caused by coexisting arterial disease in these typically elderly, often hypertensive patients. The relative infrequency of TIAs in AF patients suggests that the mechanism of ischaemia may be less often embolism from the heart and more likely due to coexisting vascular diseases. If so, the prognosis for recurrent ischaemia and the response to antithrombotic drugs might be different for AF patients with TIAs compared to those with prior ischaemic stroke. In fact, analysis of the 513 AF patients with prior cerebral ischaemia in our SPAF clinical trials showed no difference in patient features, prognosis or response to antithrombotic therapy (unpublished). The European Atrial Fibrillation Trial Investigators are also analysing a larger number of patients (PJ Koudstaal, personal communication). For now, it is prudent to manage AF patients with prior TIA in the same way as those with prior ischaemic stroke when it comes to secondary prevention.

AF patients with ‘symptomatic’ carotid stenosis

Approximately 10% of AF patients with ischaemic stroke or TIA have more than 50% stenosis at the origin of the internal carotid artery in the neck, and slightly more than half have stenosis ipsilateral to the symptomatic side of the brain. Based on estimates of attributable risk, ipsilateral stenosis of ≥ 70% is as likely to be the cause of cerebral ischaemia as embolism from the heart. Consequently, carotid endarterectomy seems reasonable for AF patients with severe ipsilateral stenosis, followed by long-term antithrombotic therapy.

Table 2  Warfarin vs. aspirin in atrial fibrillation*

<table>
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<tr>
<th></th>
<th>STROKE RATE ON ASPIRIN</th>
<th>STROKE RATE ON WARFARIN</th>
<th>RELATIVE RISK REDUCTION</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA</td>
<td>10.0%/ year</td>
<td>4.0%/ year</td>
<td>60%</td>
<td>17</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>2.7%/ year</td>
<td>1.5%/ year</td>
<td>44%</td>
<td>83</td>
</tr>
<tr>
<td>Age ≥ 75 year</td>
<td>3.4%/ year</td>
<td>1.3%/ year</td>
<td>62%</td>
<td>48</td>
</tr>
<tr>
<td>Age &lt; 75 year</td>
<td>5.9%/ year</td>
<td>3.7%/ year</td>
<td>37%</td>
<td>45</td>
</tr>
</tbody>
</table>

*NNT, the number of patients needed to treat with adjusted-dose warfarin instead of aspirin for one year to prevent one stroke.

For now, it is prudent to manage AF patients with prior TIA in the same way as those with prior ischaemic stroke when it comes to secondary prevention.

‘Leukoariosis’ or white matter thinning, is best detected by FLAIR sequences on MRI and is a strong independent predictor of warfarin-associated intracerebral bleeding in patients with non-cardioembolic brain ischaemia. This association has not been adequately studied in patients with atrial fibrillation, but probably also holds for these patients.
coagulation, although this approach is based on theory and is not supported by strong evidence. For example, in the SPAF III randomized trial, among the 30 patients with prior ischaemic stroke or TIA who had undergone carotid endarterectomy, the rate of ischaemic stroke was 11% per year (two strokes in 12 patients) in those randomized to aspirin but none in 18 anticoagulated patients (unpublished). Meagre information, to be sure, but pending additional data I routinely screen AF patients with TIA and recent ischaemic stroke for carotid stenosis, recommend endarterectomy for those with 70–99% ipsilateral stenosis, and anticoagulate them all in the long term.

What about AF patients with lacunar strokes?
As noted above, not all strokes in AF patients are due to embolism from the heart. An important minority (perhaps one-quarter) are caused by coexisting vascular disease of some sort (Fig. 2). Warfarin and aspirin are equally effective for the prevention of non-cardioembolic strokes in AF patients, but warfarin is far superior to aspirin for the prevention of cardioembolic events (Hart et al. 2000). It follows, then, that AF patients with lacunar strokes, presumed to be caused by intracranial small vessel disorders, might fare as well on aspirin as warfarin. Support for this idea is found in a recent observational case series where AF patients with presumed lacunar stroke were prospectively identified and aspirin was given to those with contraindications to, or unwillingness to take warfarin (Evans et al. 2001). Most subsequent strokes were also lacunar, and the stroke rates were similar in those receiving warfarin and aspirin. While these intriguing observations correlate nicely with pathomechanistic constructs, the relatively small numbers and non-randomized treatment assignment make it premature to withhold anticoagulation from AF patients with lacunar stroke at present. Clearly, some fraction of small subcortical infarcts in AF patients are cardioembolic (Jung et al. 2001).

Is anyone too old to be anticoagulated?
No, but it is my view that the influence of advanced age on accentuating major haemorrhage during anticoagulation has been minimized by some authors in the recent literature. Most strokes in AF patients occur in those over 75; among women over the age of 75 AF is the single most important cause of disabling stroke. Although the very elderly (≥75 years old) with AF bleed more during anticoagulation, the absolute benefit of warfarin equals or exceeds that for younger AF patients because their risk of stroke is substantially higher (Table 2) (van Walraven et al. 2002).

The ongoing UK Birmingham Atrial Fibrillation Treatment in the Aged (BAFTA) trial is of particular interest because AF patients who are aged 75 years or older are randomly assigned to adjusted-dose warfarin (target INR 2.5) vs. aspirin (75 mg/day) (Mant et al. 2002). The risks and benefits of warfarin (target INR 2–4.5) vs. aspirin (325 mg/day) had been previously assessed in the early 1990s among 385 AF patients in our SPAF II randomized trial (SPAF Investigators 1994). The intolerably high rate of intracranial haemorrhage and frequent treatment dropouts combined to make stroke rates during anticoagulation equal to those during aspirin. The BAFTA trial has three important design differences that will make it of special importance in reassessing the value of warfarin vs. aspirin in very elderly AF patients: a lower target INR, better control of hypertension (impacting on the rate of anticoagulation-associated intracerebral haemorrhage) and execution by primary care physicians in ‘real-life’ clinical circumstances.

While the optimal target INR for secondary prevention is 2.5 (target range 2–3), the range of INRs that are associated with markedly reduced stroke risk in AF patients is 1.6–3.0 (Hart 1998). For primary prevention in the very elderly (for whom the lowest effective intensity of anticoagulation is particularly important to minimize bleeding), a target INR of 2.0 (target range

**Figure 2** Some strokes in atrial fibrillation patients are not due to embolism from the heart – about 25% by best available, but not-so-good, clinical estimates.
seems most sensible, although current expert-generated guidelines generally advocate a target INR range of 2–3.

Control of hypertension in AF patients is doubly important

Hypertension is a strong, common and independent risk factor for stroke in AF patients (Hart et al. 1999b). It increases the risk of embolism by potentiating left atrial stasis mediated through left ventricular diastolic dysfunction. However, it is unclear whether sustained control of hypertension in AF patients reduces embolism, partly because left ventricular remodelling is not always reversible with treatment of elderly hypertensives. Despite the current uncertainty, it is likely that control of hypertension offers particularly large absolute reductions in stroke for AF patients.

Intracerebral bleeding is the most devastating complication of all antithrombotic treatments and is exquisitely sensitive to blood pressure control (PROGRESS Collaborative Group 2001). Hence, control of hypertension in AF patients should reduce the risk of ischaemic stroke and minimize the risk of haemorrhagic stroke that is invariably, to some extent, accentuated by antithrombotic drugs. It is high time that neurologists became more proactive in diagnosis and treatment of hypertension, and this is particularly relevant to AF patients with cerebral ischaemia treated with anticoagulants.

Immediate antithrombotic therapy for AF patients with acute cerebral ischaemia

AF patients with ischaemic stroke are, on average, older with larger hemispheric infarcts and higher early case fatality compared with stroke patients in sinus rhythm. But, contrary to the findings of earlier studies, it now appears that early recurrent ischaemic stroke is only slightly more frequent in AF compared with non-AF patients, occurring in about 5% of AF patients given aspirin during the initial 2 weeks (Saxena et al. 2001; Hart et al. 2002). It has been traditional to start heparin at once to reduce early recurrent stroke in AF, but this practice has been challenged by two randomized trials, neither showing any reduction in recurrent stroke (ischaemic and haemorrhagic) nor improvement in functional outcome (Berge et al. 2000; Saxena et al. 2001). While some may quibble about the route of administration, dosages, and which specific agent was used, the best available evidence indicates that acute ischaemic stroke patients do not benefit from heparin/heparinoids. Subgroups of AF patients can be suggested who might benefit from immediate anticoagulation (e.g. those with small infarcts less prone to haemorrhagic transformation, those with atrial appendage thrombi detected by transoesophageal echocardiography, etc.), but this remains speculative without randomised trial evidence and does not justify treatment. Conversely, early initiation of aspirin in AF patients with acute ischaemic stroke was associated with convincing trends toward a modest reduction in early recurrent stroke and improved functional outcome in the combined analysis of the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (Hart et al. 2002).

Should AF patients with recent TIAs be managed any differently? The fact that the short-term prognosis for recurrent ischaemia after TIA is no different in AF patients compared with those in sinus rhythm (Johnston et al. 2003; Johnston et al. 2000) and the lack of evidence from randomized trials, makes any recommendations difficult. In the IST, heparin 12 500 units given subcutaneously twice daily to AF patients with acute stroke reduced early recurrent ischaemic stroke by 50%, but this benefit was offset by the increased risk of intracerebral haemorrhage (Saxena et al. 2001). In the IST, the frequency of intracerebral haemorrhage was directly related to infarct size (Leonardi-Bee et al. 2000). It is high time that neurologists became more proactive in diagnosis and treatment of hypertension, and this is particularly relevant to AF patients with cerebral ischaemia treated with anticoagulants.
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2002). Hypothetically then, AF patients with TIA given heparin should have a low likelihood of intracerebral haemorrhage to offset the potential reduction in early ischaemic stroke. Of note, the Heparin in Acute Embolic Stroke Trial showed no suggestion of reduction in early ischaemic stroke by anticoagulation (Berge et al. 2000; Hart et al. 2002).

Some authors advocate immediate heparin anticoagulation of AF patients with TIA based on the presumed cardioembolic pathogenesis, low likelihood of haemorrhagic worsening, and the reduction in early recurrent ischaemic stroke by heparin among AF patients in the IST (Johnston 2002). While this is not unreasonable in the absence of direct clinical trial data, because of the uncertainties in the balance of benefit and risk and the estimated large numbers-needed-to-treat (> 50) in unselected patients I favour aspirin for most AF patients with recent TIA, and then starting warfarin for long-term secondary prevention as soon as possible. In selected AF patients with TIA or minor stroke likely to be at higher than average risk of early recurrent embolism (e.g. atrial thrombus known to be present by transoesophageal echocardiography, multiple recent embolic events), I use intravenous heparin despite the lack of solid evidence.

ONGOING CLINICAL RESEARCH: STAY TUNED!

We still need more effective antithrombotic drugs than aspirin, and safer and easier to use treatments than adjusted-dose warfarin. Ximelagatran, a novel oral direct thrombin inhibitor, is being compared to adjusted-dose warfarin in two international mega-trials involving over 7300 AF patients (SPORTIF III and V), with results anticipated in late 2003. Early results are promising. Ongoing trials are testing combination antiplatelet therapy (aspirin and clopidogrel) and other novel antithrombotic agents, and the results are anticipated during the next several years from eight ongoing clinical trials enrolling over 20 000 AF patients. From a neglected cause of major stroke 15 years ago, AF has become a focus of intensive clinical research that has lead to effective, well-tolerated stroke prevention therapies for millions of people. The challenge remains to apply these therapies optimally in routine clinical practice.
REFERENCES

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