Letters to the Editor

Assessment of risk of thromboembolism in atrial fibrillation: which patients should be anticoagulated?

In his Editorial, Kulbertus[1] highlights the uncertainties facing many clinicians over choice of antithrombotic therapy for patients with atrial fibrillation.

It is often forgotten that most patients with atrial fibrillation are managed in the community. Indeed, our general practice survey suggests that only a third of patients with atrial fibrillation have presented to hospital[2], and that most general practitioners, who manage the majority of patients with atrial fibrillation, have real concerns over how to identify such patients, who might be at high risk of stroke and thromboembolism. Based mainly upon clinical criteria from the pooled analysis of the Atrial Fibrillation Investigators, most patients with atrial fibrillation can be classified into ‘high’, ‘moderate’ and ‘low’ risk patients, and such a risk stratification for thromboprophylaxis in atrial fibrillation has been successfully applied to a general practice screening programme[3,4]. These simplified guidelines for risk stratification are summarized in Table 1.

Kulbertus[3] also raises concerns about the risks of bleeding with anticoagulation. Indeed, the atrial fibrillation anticoagulation trials were essentially ‘packages of care’ that included drugs, careful monitoring and follow-up of highly selected, well-motivated patients/investigators. As many patients were excluded after initial assessments for the absence of contraindications, the ratio of anti-thrombotic benefit to bleeding risk may perhaps be lower in clinical practice than in the published trials. Nevertheless, the same arguments can be made for many trials, especially with regard to the application to everyday reality in our clinical practice. It is often forgotten that many strokes in the warfarin-treated group occurred whilst the international normalized ratios were subtherapeutic; a counter-argument may therefore be that the efficacy of warfarin for thromboprophylaxis was actually underestimated!

Kulbertus[1] enthusiastically lists various transthoracic and transoesophageal echocardiographic features that are indicative of an increased risk of stroke and thromboembolism. Many general practitioners, at least in the United Kingdom, have difficulties of access to transthoracic echocardiography, let alone transoesophageal echocardiography, and the question also arises whether echocardiography services can cope with the vast majority of patients with atrial fibrillation who are managed in general practice, many of whom may be asymptomatic[2]. Contrary to what Kulbertus[1] suggests, isolated left atrial enlargement may not be an independent risk factor for increased stroke risk. The most recent meta-analysis from the Atrial Fibrillation Investigators of 1066 patients from three clinical trials suggested that echocardiography, merely refined clinical risk stratification schema, with only moderate to severe left ventricular systolic dysfunction, via two-dimensional transthoracic echocardiography, independently predicting stroke risk in patients with atrial fibrillation[5]. Evidence for the complementary role of echocardiography in stratifying clinical risk provided by data from the Newcastle survey, where 4.7% of participants aged ≥65 years in a general practice screening survey had atrial fibrillation, and with application of the Atrial Fibrillation Investigators clinical criteria, 49% would require warfarin; however, echocardiography was only useful in the minority of mainly younger subjects with a low risk of stroke according to clinical risk factors[4]. Indeed, a further study from general practice by Cantley et al[6] concluded that in no cases did echocardiography alter management decisions with respect to antithrombotic therapy, throwing doubt on the need for ‘open access’ echocardiography purely to assess the risk of thromboembolism in atrial fibrillation. Hopefully, clinicians would only rarely need to proceed to transoesophageal echocardiography to assist risk stratification, but in the SPAF-III (Stroke Prevention in Atrial Fibrillation III study) transoesophageal echocardiography substudy, stroke and thromboembolism were correlated with dense spontaneous echocontrast, left atrial

Table 1 Risk stratification and anticoagulation in non-valvular atrial fibrillation (NVAF)

<table>
<thead>
<tr>
<th>Assess risk</th>
<th>Treatment</th>
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<tr>
<td>(1) High risk (annual risk of CVA=8–12%)</td>
<td>• High risk: use warfarin (target international normalized ratio 2.0–3.0) if no contraindications and possible in practice.</td>
</tr>
<tr>
<td>• All patients with NVAF and previous TIA or CVA</td>
<td>• Moderate risk: Either warfarin or aspirin. In view of insufficient clearcut evidence, treatment may be decided on individual cases. Referral and echocardiography may help.</td>
</tr>
<tr>
<td>• All patients aged 75 and over with NVAF and diabetes and/or hypertension</td>
<td>• Low risk (annual risk of CVA=1%)</td>
</tr>
<tr>
<td>• All patients with clinical evidence of valve disease, heart failure, thyroid disease and/or impaired LV function on echocardiography*</td>
<td>• All other patients under 65 with NVAF with no history of embolism, hypertension, diabetes or other clinical risk factors.</td>
</tr>
<tr>
<td>• All patients under 65 with NRAF and clinical risk factors: diabetes, hypertension, peripheral arterial disease, ischaemic heart disease.</td>
<td></td>
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<tr>
<td>• All patients over 65 with NVAF who have not been identified in high risk group.</td>
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<tr>
<td>(2) Moderate risk (annual risk of CVA=4%)</td>
<td></td>
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<tr>
<td>• All other patients under 65 with NVAF with no history of embolism, hypertension, diabetes or other clinical risk factors.</td>
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*Treatment recommendations based upon the Stroke Prevention in Atrial Fibrillation I (SPAF-I) study: NVAF=nonsurgical atrial fibrillation; NRAF=nonsurgical atrial fibrillation; LV=function; CVA=cerebrovascular accident; TIA=transient ischaemic attack.

References


appendage thrombus and complex aortic plaques. Reduced left atrial appendage flow velocities can be added to this list.

As highlighted by Kulbertus, atrial fibrillation thromboprophylaxis is a particular problem in the elderly. Whilst stroke risk increases with age, this is a particular problem in the elderly. In the SPAF-II study, there was an increased risk of intracranial haemorrhage in the warfarin group, particularly in patients aged over 75 years (1.8%/year); however, this rate was substantially higher than that reported in the initial five trials (on average 0.3%/year), perhaps reflecting the higher intensity of anticoagulation in the SPAF-II study (international normalized ratio up to 4.5). Whilst some studies have suggested that the risk of bleeding with anticoagulation increases with age, this finding is not universal. Whilst the target international normalized ratio for anticoagulation in non-valvular atrial fibrillation is between 2.0 to 3.0, providing maximal thromboprophylaxis with minimal bleeding risk, an international normalized ratio between 1.6–2.5 can provide substantial, if partial efficacy (nearly 90% of the highest intensities) for thromboprophylaxis.

Given some uncertainty about the safety of international normalized ratios >3.0, especially in elderly atrial fibrillation patients, a target international normalized ratio of 2.0 (range 1.6–2.5) may perhaps be a reasonable compromise between efficacy and toxicity for the elderly.

There are continuing concerns about which patients we should anticoagulate, and the necessity for vigorously attempting risk stratification for thromboprophylaxis in atrial fibrillation, even if largely using clinical criteria; at least the 'high risk' patients, who would benefit most from warfarin, could be targeted for treatment, after careful assessment for contraindications to therapy. As with many therapeutic decisions in clinical medicine, it is often a question of risk–benefit ratio.

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References

Article No. euh.1999.1849, available online at http://www.idealibrary.com

A reply
I wish to thank Doctor Lip for his interest in the Editorial that I wrote for this Journal. I found his comments most useful. First of all, he draws the reader’s attention to important recent publications by his own group, whose expertise in the management of atrial fibrillation in the community is well recognized. His remark that the efficacy of warfarin could have been underestimated in the large clinical trials of atrial fibrillation is, of course, sound; this danger is, in fact, inherent to the protocol of the vast majority of clinical trials nowadays. Lip’s suggestion that a target international normalized ratio of 2 may perhaps be a reasonable compromise between efficacy and toxicity in the elderly is also interesting; it deserves consideration and ought to be tested.

What I disagreed with in Lip’s letter was his use of the word ‘enthusiastic’ when he refers to my listing of echocardiographic features indicative of an increased risk of thromboembolism. If I appeared as overly emphasizing echocardiography, this was not my intention. In fact, if Lip read the strategy that I proposed at the end of my Editorial, he may have noticed that my own risk stratification is, with few minor exceptions, identical to his and exclusively based on simple clinical factors. Admittedly I have a problem with atrial fibrillation patients aged 60 (65)–75 with no apparent risk factor. For this subgroup, I think that a refinement of our clinical risk assessment is needed. I think that Lip will not disagree, since his own recommendation for this particular category of patients reads: ‘In view of insufficient clear-cut evidence, treatment may be decided on individual cases. Referral and echocardiography may help’.

My suggestion was that a new study limited to that subgroup and incorporating data from the echocardiogram (transesophageal echocardiography) would be worthwhile. After all, if we want to resort to echo, it might be useful to know exactly what we have to look for and how to best interpret the findings. Patients with atrial fibrillation and no clinical risk factor other than an age between 60 (or 65)–75 are not uncommon, but they do not represent a host either. Should transthoracic echocardiography/transoesophageal echocardiography be demonstrated to contribute valuably to their risk assessment, their number is unlikely to satiate echo units, at least in my country. It is recognized that regional differences may exist in the access to echocardiography; this does not release those who have easy access to it from their duty to try to make the best possible use of a technique which is widely at their disposal.

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