The influence of randomized trials on the use of anticoagulants for atrial fibrillation

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Abstract

Introduction: anticoagulants and anti-platelet drugs have been shown in randomized trials to reduce the risk of stroke in patients with atrial fibrillation (AF). We therefore investigated their use in patients known to be in AF before a stroke, transient ischaemic attack (either cerebral or ocular) or retinal artery occlusion to assess the influence of trials on clinical practice.

Methods: inpatients and outpatients with acute stroke, transient ischaemic attack or retinal artery occlusion were prospectively identified by a stroke physician from 1990 to 1997. The presence or absence of AF before the vascular event, and prior use of anticoagulant and anti-platelet drugs were recorded at the time of the assessment and verified using information from general practitioner and hospital case notes.

Results: of 1934 patients with stroke or retinal artery occlusion, 191 (10%) were in AF before their ischaemic event. Anticoagulants had been used in 40 (21%) of these, but only in 32 (2%) of the 1743 patients in sinus rhythm [odds ratio (OR) 14.2, 95% confidence interval (CI) 8.6–23.2]. Anti-platelet drugs had been used in 62 (32%) of those with AF compared with 500 (30%) of those in sinus rhythm (OR 1.2, 95% CI 0.9–1.64). Of the 161 patients in AF without contraindications to anticoagulants, only 36 (22%) were taking them. Although there was a statistically significant increase in anticoagulant use from 8% in 1990 to 23% in 1996, this could be explained solely by a fall in the age of the patients referred to our hospital.

Conclusion: anticoagulation is probably under-used in AF. We found no conclusive evidence that anticoagulation trials have influenced clinical practice. This raises issues about the dissemination and implementation of trial results.

Keywords: atrial fibrillation, inpatients, sinus rhythm, stroke

Introduction

The annual risk of stroke in patients with atrial fibrillation (AF) is 5%, which is five times higher than the risk for patients in sinus rhythm [1]. Six large randomized trials of primary prevention have shown that anticoagulation reduces the risk of stroke in patients with AF by about two-thirds [2–7].

Patients in AF with a recent minor ischaemic stroke or transient ischaemic attack have a higher absolute risk of recurrent stroke than those in AF without a previous event [8]. In these symptomatic patients, anticoagulation also reduces the annual risk of stroke from 12% to 4% [8].

For patients in AF with a previous minor stroke or transient ischaemic attack, aspirin reduces the annual risk of vascular death, non-fatal stroke, myocardial infarction or systemic embolism from 19 to 15% [8].

The role of aspirin in the primary prevention of stroke in AF is less certain, although it has been investigated in two trials [2, 7]. One of these found a 50% reduction in stroke risk compared with placebo, although confidence intervals were wide [7]. The other failed to demonstrate a reduction in stroke risk, but the risk of combined outcome events (stroke, systemic embolism and death) was reduced by about one-quarter [2]. In the absence of contraindications, warfarin is the best treatment for the primary prevention of stroke in
patients with AF. Aspirin is less effective, but should be considered when anticoagulation with warfarin is contraindicated [9].

Despite the benefits of anticoagulation, previous hospital and community studies have demonstrated that not all patients with AF receive it [10–15]. This cannot be entirely explained by the presence of contraindications. For example, in one community study, only one-third of patients had contraindications, and only one-fifth of those without contraindications were receiving anticoagulation [15].

Given that AF is an important risk factor for cerebral embolism and stroke, we sought to identify how many patients with acute stroke, transient ischaemic attack or retinal artery occlusion seen at our hospital were known to be in AF before their ischaemic event, and how many were receiving prophylactic anticoagulation or anti-platelet drugs before the event. We also wanted to investigate whether there had been any change in anticoagulant use over time which could have occurred in response to the publication of the anticoagulation trials. If the results of anticoagulation trials have been disseminated and fully implemented, then one would expect that most patients with AF who had no contraindications would now be taking anticoagulants or anti-platelet drugs.

Methods

Patients with acute stroke, cerebral transient ischaemic attack, ocular transient ischaemic attack and retinal artery occlusion who were admitted to our hospital from October 1990 to April 1997 were identified by a stroke physician by regular discussion with ward doctors and perusal of admission records. From 1994, outpatients with acute stroke, transient ischaemic attack or retinal artery occlusion referred to neurovascular clinics were also assessed. The stroke physician recorded whether the patient had been in AF before their event, using hospital case notes, previous electrocardiographs and information from the general practitioner records when required. Use of anticoagulants and anti-platelet drugs before the event was recorded from hospital and general practitioner records. The stroke physician also recorded the presence of anaemia and thrombocytopenia, alcohol abuse, daily use of non-steroidal anti-inflammatory drugs and severe impairment of renal function. Hospital notes were retrospectively reviewed for the presence of other contraindications: recurrent falls, difficulty with compliance, thrombotic disorders and active bleeding (e.g. haematemesis, rectal bleeding, haematuria [13]). Computed tomography (CT) brain scan was arranged whenever possible for patients with acute stroke. Data were entered onto a computer data base (Lothian Stroke Register) for subsequent analysis.

Odds ratios (ORs), with 95% confidence intervals, were calculated in order to compare the use of anticoagulants and anti-platelet drugs in patients with AF and sinus rhythm. t-tests were used where appropriate. Logistic regression was used to investigate which factors might account for any observed changes in the use of anticoagulants and anti-platelet drugs over time.

Results

Of the 1945 patients registered with general practitioners in 180 different practices assessed, 1549 (80%) had suffered an acute stroke, 393 (20%) a transient ischaemic attack and 48 (2%) a retinal artery occlusion. These categories were not mutually exclusive, with 45 patients having more than one diagnosis. Of the 1549 patients with acute stroke, 1348 (87%) had a brain CT. This showed primary intracerebral haemorrhage in 105 (8%), was normal in 420 (31%) and showed an infarct or an irrelevant lesion in the rest. Of the 396 patients with a transient ischaemic attack or retinal artery occlusion, 163 (41%) had CT. This showed a haemorrhage in one patient and was normal or showed an infarct in the rest. For the purposes of this study, patients with no CT were assumed to have suffered a cerebral infarct. There were 11 patients (two primary intracerebral haemorrhage, nine cerebral infarcts) with missing data on drugs or cardiac rhythm before the event. These were excluded from the analyses.

Of the 104 patients with primary intracerebral haemorrhage on CT, 11 (11%) were known to be in AF before their stroke. Five (45%) of these were taking anticoagulants, four (36%) were taking anti-platelet drugs and two (18%) neither anticoagulants nor anti-platelet drugs. For the five patients taking anti-coagulants, the mean international normalized ratio (INR) was 2.6 (range 2.4–3.1).

Of the 1934 patients with data for analysis, 191 (10%) were known to be in AF before the stroke. Their use of anticoagulant and anti-platelet drugs is shown in Table 1. Of the 191 patients in AF, 64 (34%) had sustained a previous transient ischaemic attack or stroke. Anticoagulants were used in 13 of these (20%) compared with 27 (21%) of the 127 with no previous transient ischaemic attack or stroke (OR 0.9, 0.4–2.0).

Among the 191 patients in AF there were no contraindications to anticoagulant use in 161 (84%), but only 36 (22%) of these were taking anticoagulants. Of the 30 patients who had contraindications, four (13%) were taking anticoagulants. The difference in anticoagulant use between those with and without contraindications was not significant (OR 0.5, 0.2–1.6).

Tables 2 and 3 show the characteristics of the AF patients taking anticoagulants and anti-platelet drugs respectively. Those taking anticoagulants were
significantly younger (mean age 69) than those not taking anticoagulants (mean age 78, \( P < 0.05 \), unpaired \( t \)-test), and were more likely to have clinical valvular heart disease (any murmur on clinical examination except a flow murmur; OR 4.5; 2.2–9.3). Those taking anti-platelet drugs were more likely to have had a previous stroke or transient ischaemic attack (OR 2.9; 1.5–5.5) and to have ischaemic heart disease (OR 2.9; 1.6–5.4) than those not taking anti-platelet drugs.

Over the study period, the proportion of patients with AF fell from 16% in 1990 to 10% in 1996. Figure 1 demonstrates the change in use of anticoagulant and anti-platelet therapy for patients with acute stroke over time. The regression line for anticoagulant use in AF was significantly different from that for sinus rhythm, with anticoagulant use increasing from 8% in 1990 to 23% in 1996. There was also a significant rise in anti-platelet use over time for patients in both AF and sinus rhythm, but no significant difference between the slope of the regression lines for AF and sinus rhythm (OR 1.26, 0.91–1.74).

Logistic regression was used to investigate whether other factors (previous vascular events or vascular disease, stroke risk factors, valvular heart disease, age, inpatient or outpatient status, living alone, being currently employed or an Oxford Handicap score of 0–2) might account for the rise in anticoagulation use for AF between 1990 and 1996. Age and valvular heart disease were the only significant factors. Although valvular heart disease was significantly related to anticoagulant use, it was independent of year and therefore does not account for the rise in anticoagulation. The mean age (standard deviation) was 73.5 years (12.1) in 1990 and 67.0 (12.7) in 1996. When age was included in the regression model, year alone was not significant (OR 1.22, 0.95–1.56).

**Discussion**

There was a significant rise in anticoagulant use during the study period, but there was also a fall in the mean age of patients in AF. This probably reflects changes in referral patterns to evolving stroke services (which incorporate a specialist stroke unit and neurovascular outpatient clinics) and the closure of the accident and emergency department. A less likely explanation for the fall in age during the study period is that elderly patients living at home were anticoagulated in accordance with the trial results and were therefore less likely to present...
with a stroke or transient ischaemic attack. When age was taken into account, the year alone was not an independent predictor of anticoagulant use, although there was a non-significant trend towards a rise over time. The absence of a significant rise after age was taken into account may reflect the relatively small number of patients.

Although the presence of contraindications (16%) might have explained the low rate (20%) of anticoagulation, it cannot be the whole explanation, even

Table 3. Use of anti-platelet drugs in the 191 patients in atrial fibrillation (of the 129 patients not taking anti-platelet drugs, 34 (26%) were taking anticoagulants)

<table>
<thead>
<tr>
<th>Use of anti-platelets</th>
<th>Yes ((n = 62))</th>
<th>No ((n = 129))</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>31 (50%)</td>
<td>63 (49%)</td>
<td>1.0 (0.6, 1.9)</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>31 (50%)</td>
<td>33 (26%)</td>
<td>2.9 (1.5, 5.5) *</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>34 (55%)</td>
<td>38 (29%)</td>
<td>2.9 (1.6, 5.4) *</td>
</tr>
<tr>
<td>Hypertension before event</td>
<td>28 (45%)</td>
<td>58 (45%)</td>
<td>1.0 (0.5, 1.9)</td>
</tr>
<tr>
<td>Inpatient at time of event</td>
<td>48 (77%)</td>
<td>109 (84%)</td>
<td>0.6 (0.3, 1.3)</td>
</tr>
<tr>
<td>Living alone</td>
<td>29 (47%)</td>
<td>50 (39%)</td>
<td>1.4 (0.8, 2.6)</td>
</tr>
<tr>
<td>Employed</td>
<td>1 (2%)</td>
<td>9 (7%)</td>
<td>0.2 (0.0, 1.8)</td>
</tr>
<tr>
<td>Independent before event^b</td>
<td>49 (79%)</td>
<td>105 (81%)</td>
<td>0.9 (0.4, 1.8)</td>
</tr>
<tr>
<td>Valvular heart disease^c</td>
<td>19 (31%)</td>
<td>39 (30%)</td>
<td>1.0 (0.5, 2.0)</td>
</tr>
</tbody>
</table>

\*P < 0.05.
\^bOxford Handicap score 0–2.
\^cDefined as any murmur on clinical examination except a simple flow murmur.

OR, odds ratio; CI, confidence interval; TIA, transient ischaemic attack.

Figure 1. Percentage of acute stroke patients in AF (●) and sinus rhythm (○) receiving anticoagulant (---) and anti-platelet (—) treatment, by year. Patients with transient ischaemic attack and retinal artery occlusion only (396) were excluded as they were registered only from 1994 onwards. Eleven patients with missing data and nine patients registered in 1997 are not included.
though we might have underestimated the frequency of contraindications. Anticoagulation for atrial fibrillation is probably under-used: only 32% of AF patients were receiving aspirin before their event, which is surprising given that aspirin has fewer side effects than warfarin and reduces the risk of stroke by about one-quarter in patients with known ischaemic heart disease and peripheral vascular disease [16].

Our low rate of anticoagulation is similar to those reported in UK community studies and hospital series [10–15]. This may reflect concerns about the generalizability of clinical trials or concerns about the safety and practicality of anticoagulation [17, 18]. Our cohort was more likely to include patients where anticoagulation had been ineffective or had not been given, which means that our series may not be representative of all AF patients at home. A study of community patients before and after publication of the trials would be required to investigate the influence of the trials on anticoagulation prescription for AF.

Publication of trial results alone is not enough to change practice: formal guidelines tend to be more effective [19]. However, a recent survey has demonstrated widespread non-systematic production of guidelines for AF, which could lead to considerable variation in practice [20]. There is a need for well-funded programmes of guideline development such as the Scottish Intercollegiate Guideline Network. Further work is required to ensure that the guidelines are implemented. It is also essential that the infrastructure for safely monitoring warfarin therapy is in place to replicate the results achieved in trials.

Key points

- Anticoagulation is probably under-used in atrial fibrillation.
- In hospital patients with stroke, transient ischaemic attack or retinal artery occlusion, we found no conclusive evidence that the anticoagulation trials have influenced the prescription of anticoagulants.
- Further work is required to investigate ways to implement the results of the trials in clinical practice.

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References


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