Should Stroke Subtype Influence Anticoagulation Decisions to Prevent Recurrence in Stroke Patients With Atrial Fibrillation?

Andrew Evans, MRCP; Inigo Perez, MD; Gloria Yu, FRCP; Lalit Kalra, PhD, MRCP

Background and Purpose—Long-term anticoagulation is routinely used for secondary stroke prevention in atrial fibrillation, often regardless of stroke subtype. Although the role of warfarin in cardioembolic stroke is established, it may not prevent recurrence in other stroke subtypes, even in the presence of atrial fibrillation.

Methods—This was a 2-year, prospective, intervention study conducted in a district general hospital. Participants included 386 acute stroke patients with atrial fibrillation. Subjects were characterized for stroke subtype on clinical, neuroimaging, carotid ultrasonographic, and echocardiographic criteria. Eligible patients were treated with adjusted-dose warfarin (international normalized ratio, 2.0 to 3.0). Aspirin (75 to 300 mg/d) was used in patients with contraindications or those who refused anticoagulation. The main outcome measures were rate of recurrent stroke by subtype and major and minor bleeding complications.

Results—The aspirin group (n=172) was comparable to the warfarin group (n=214) in terms of age, sex, risk factors, and initial stroke subtype. The rate of recurrent stroke was higher (9.5% versus 4.9%, P<0.02) but that of major bleeding was lower (0.6% versus 2.5%, P<0.05) with aspirin. The increased stroke rate with aspirin was due predominantly to cardioembolic recurrence in patients presenting initially with cardioembolic stroke (8.4% versus 1.9%, P<0.01). The recurrence rate in aspirin-treated patients who presented with lacunar stroke and atrial fibrillation was similar to that seen in patients receiving warfarin (8.8% versus 8.9%).

Conclusions—In this cohort of stroke patients with atrial fibrillation, anticoagulation was superior to aspirin in preventing cardioembolic but not lacunar recurrence. Determination of stroke subtype may be important in anticoagulation decisions for secondary prevention, and further studies are required. (Stroke. 2001;32:2828-2832.)

Key Words: anticoagulants ■ antiplatelet agents ■ lacunar infarction ■ stroke prevention ■ stroke, cardioembolic

Ischemic stroke patients with atrial fibrillation are at high risk of stroke recurrence, which can be dramatically reduced by long-term anticoagulation soon after the presenting event.1,2 The use of adjusted-dose warfarin for stroke patients with atrial fibrillation who do not have significant bleeding risk has been advocated in several professional guidelines,3–6 and the benefit has been demonstrated in clinical practice.7 However, not all strokes in patients with atrial fibrillation are cardioembolic in origin,7–9 and some evidence suggests that warfarin may not prevent noncardioembolic strokes.7,9,10 It has also been shown that anticoagulation in patients with small-vessel cerebrovascular disease carries a higher risk of intracranial hemorrhage.11 Neither the definitive study on the effectiveness of anticoagulation2 nor subsequent recommendations3–6 on secondary prevention of stroke in atrial fibrillation discriminate on the basis of stroke subtype, and it is possible that some patients who have nonembolic strokes may be put at unnecessary risk by long-term anticoagulation. These risks could be significantly reduced and implementation in clinical practice could be enhanced by targeting anticoagulation to those deriving the greatest benefit12 and prescribing aspirin to other subtypes despite the presence of atrial fibrillation.

The objective of this prospective cohort study was to determine whether the subtype of the presenting stroke influenced the effectiveness of long-term anticoagulation in preventing recurrence.

Subjects and Methods

Patients
This study was undertaken in ischemic stroke patients admitted to a district general hospital over 4 years. Inclusion criteria were clinical ischemic stroke confirmed by CT scanning and atrial fibrillation confirmed on ECG. Patients who were unwilling to participate or who had contraindications to both anticoagulation and aspirin were excluded.

Stroke Subtype Assignment
All patients were assessed by use of standardized history and examination, CT scanning, extracranial carotid duplex ultrasonography, echocardiography, and laboratory tests. Stroke subtypes were
based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST)\textsuperscript{13} and the Stroke Prevention in Atrial Fibrillation (SPAF)\textsuperscript{9} subtype classification systems and defined as follows. Lacunar was defined as a clinical lacunar syndrome\textsuperscript{14} with either small, deep, oval white matter or basal ganglia infarcts $<1.5$ cm in diameter, periventricular hypodensity, or no lesion on CT scanning. Cardiogenic embolic was defined as a cortical syndrome and/or infarct $>1.5$ cm in diameter on CT scan in the presence of an abnormal echocardiogram\textsuperscript{3} and in the absence of a $50\%$ stenosis of the relevant carotid artery. Strokes were classified as undetermined when (1) cortical syndrome was present with infarct $>1.5$ cm in diameter and $>50\%$ stenosis of relevant carotid artery, (2) the CT was suggestive of lacunar infarction but without classic clinical lacunar syndrome, or (3) $>1$ cause was equally likely.

Stroke subtype was categorized at 2 levels: by the admitting stroke team and by an independent expert on the basis of masked clinical details and investigations. Patients in whom it was not possible or reach consensus were placed in the undetermined group.

**Antithrombotic Assignment**

Secondary prevention was undertaken in accordance with existing guidelines.\textsuperscript{3–6} All patients were considered for adjusted-dose warfarin if they did not have contraindications to anticoagulation. The contraindications were coagulopathy or thrombocytopenia, gastrointestinal bleeding in the 6 months before stroke, previous cerebral hemorrhage, severe uncontrolled hypertension, need for regular nonsteroidal antiinflammatory drugs, excessive alcohol intake, dementia, recurrent falls, severe dependent stroke (modified Rankin score $>3$),\textsuperscript{13} and uncontrolled epilepsy. Patients with poor drug or clinic compliance or who were unwilling to consent to long-term anticoagulation were also excluded.

Contraindications to aspirin were defined as coagulopathy, thrombocytopenia, recent upper gastrointestinal bleeding, active peptic ulceration, or aspirin allergy.

**Interventions**

Patients who had no contraindications to anticoagulation were treated with adjusted-dose warfarin with a target international normalized ratio (INR) of $2.0$ to $3.0$. Patients with mild to moderate neurological deficits and CT lesions of $<2.5$ cm were anticoagulated within 72 hours of stroke onset. Anticoagulation was begun after 2 weeks in patients with larger infarcts. Warfarin control was performed by local anticoagulation services after discharge from the ward.

Patients who had contraindications to warfarin but not to antplatelet agents were treated with aspirin $75$ to $300$ mg/d as soon as cerebral hemorrhage had been excluded on CT scanning. Patients who were initially treated with warfarin but discontinued for reasons of choice, compliance, or logistics but not for study end points were treated with aspirin and then followed up in the aspirin group.

**Follow-Up**

Patients were followed up for 2 years after the relevant treatment was begun. Patients were assessed every 6 months for neurological symptoms and signs and for episodes of bleeding. Hospital records were consulted to document admissions or events that may not have been recalled by the patient. General practitioners were contacted for any additional information. Patients who had defaulted from clinic attendance were contacted by telephone and visited at home if necessary. This enabled $100\%$ completion of follow-up assessments.

**End Points and Statistical Analyses**

Recurrent stroke was diagnosed on the basis of clinical and neuroimaging examinations and were classified by subtype. The classification of stroke subtypes was validated by an independent observer not involved in original assessments. Recurrent stroke patients were assessed for outcome at 3 months with the modified Rankin score (5 and 6, severe disability or death; 3 and 4, moderate disability; 0 to 2, no to mild disability). Intracerebral hemorrhages were counted separately.

### TABLE 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Clinical stroke subtype</th>
<th>Warfarin (n=214)</th>
<th>Aspirin (n=172)</th>
<th>Difference (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolic</td>
<td>133 (62)</td>
<td>104 (60)</td>
<td>2 (−8–12)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>38 (18)</td>
<td>36 (21)</td>
<td>−3 (−11–5)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>43 (20)</td>
<td>32 (19)</td>
<td>−7 (−7–9)</td>
</tr>
<tr>
<td>Median duration of follow-up, $y$</td>
<td>2.1</td>
<td>2.2</td>
<td>0.1 (0–3)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; TIA, transient ischemic attack.

All deaths were recorded, and a cause was assigned on the basis of available clinical information. Deaths resulting from cerebrovascular causes were excluded to prevent double counting. All bleeding events were recorded. Major bleeding was defined as fatal bleeding or bleeding leading to hospitalization, emergency procedures, or urgent transfusion. All other bleeds were classified as minor.

Baseline variables were presented as median or proportion as appropriate. Comparisons between groups were made with the Mann-Whitney $U$ test in the case of skewed distributions or the $x^2$ test, as appropriate. The on-treatment event rate per patient-year was calculated, and the exact Poisson CIs were used for comparisons of clinical outcomes because of the small numbers (resulting from low incidence) in these groups. The differences in rates, 95% CIs, and statistical significance were calculated with the Z test.

**Results**

**Baseline Characteristics**

We treated 214 patients with warfarin and 172 patients with aspirin (123 because of defined contraindications; 49 because of choice, compliance, logistics, or patient/physician preference). The 2 treatment groups were comparable for age, sex, risk factor profile, and stroke subtype (Table 1). Patients on warfarin had a mean INR of $2.49\pm0.26$ and spent an average of $66\%$ of the time within the target INR range of $2.0$ to $3.0$.

**End Points**

The recurrent stroke rate in patients being treated with aspirin was significantly higher than in those on warfarin (Table 2). There was no significant difference in the rate of intracranial hemorrhage on either treatment. Differences between groups in overall mortality, death from stroke, cardiac death, noncerebral bleeding, or nonvascular death were all not significant. There were significantly fewer bleeding events in the aspirin group than in the warfarin group. The differences were most marked for minor bleeds, but there was still an excess of major bleeds in the warfarin group.
TABLE 3. Recurrence by Stroke Subtype and Treatment Allocation

<table>
<thead>
<tr>
<th>Initial Stroke Subtype</th>
<th>Treatment</th>
<th>Patients, n</th>
<th>Patient-years</th>
<th>Recurrent Strokes, n</th>
<th>Event rate (95% CI), %</th>
<th>Cardioembolic</th>
<th>Undetermined</th>
<th>Lacunar</th>
<th>Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolic</td>
<td>Warfarin</td>
<td>133</td>
<td>269</td>
<td>9</td>
<td>3.3 (1.2–5.5)</td>
<td>5</td>
<td>1.9 (0.2–3.5)</td>
<td>2</td>
<td>0.7 (0–1.8)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>104</td>
<td>214</td>
<td>23</td>
<td>10.7 (6.3–15.1)</td>
<td>18</td>
<td>8.4 (4.5–12.3)</td>
<td>3</td>
<td>1.4 (0–3.0)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>Warfarin</td>
<td>38</td>
<td>77</td>
<td>4</td>
<td>5.2 (0.1–10.3)</td>
<td>1</td>
<td>1.3 (0–3.8)</td>
<td>1</td>
<td>1.3 (0–3.8)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>36</td>
<td>77</td>
<td>5</td>
<td>6.4 (0.8–12.2)</td>
<td>2</td>
<td>2.6 (0–6.0)</td>
<td>1</td>
<td>1.3 (0–3.8)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>Warfarin</td>
<td>43</td>
<td>102</td>
<td>9</td>
<td>8.8 (3.1–14.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.0 (0–2.9)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>32</td>
<td>67</td>
<td>6</td>
<td>8.9 (1.8–16.1)</td>
<td>2</td>
<td>3.0 (0–7.0)</td>
<td>1</td>
<td>1.5 (0–4.4)</td>
</tr>
<tr>
<td>Total</td>
<td>Warfarin</td>
<td>214</td>
<td>448</td>
<td>22</td>
<td>4.9 (2.9–7.0)</td>
<td>6</td>
<td>1.3 (0.3–2.4)</td>
<td>4</td>
<td>0.9 (0–3.3)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>172</td>
<td>358</td>
<td>34</td>
<td>9.5 (6.3–12.7)</td>
<td>22</td>
<td>6.1 (3.6–8.7)</td>
<td>5</td>
<td>1.4 (0.2–2.6)</td>
</tr>
</tbody>
</table>

Rates expressed as events per hundred patient-years (%) with exact Poisson CIs.
prevalence of both atrial fibrillation\textsuperscript{16} and small-vessel disease\textsuperscript{17} increases with age and because there is a risk that some patients may be exposed to the risks of anticoagulation and intracerebral hemorrhage\textsuperscript{11} without necessarily benefiting from the treatment. Although it is widely recognized that stroke is a heterogeneous condition with diverse origin, little attention has been paid to stroke subtyping until recently. The importance of stroke subtype and targeting of secondary prevention to the individual who has had a relevant stroke rather than any stroke has been recognized in patients with carotid stenosis.\textsuperscript{18,19} It is likely that subtyping according to possible origin may be equally important in stroke patients with atrial fibrillation. The current orthodoxy of “stroke and atrial fibrillation, therefore warfarin” has the virtue of simplicity, but it may not be to the benefit of all.

The uncertainty of advantages of anticoagulation over aspirin in patients with nonvalvular atrial fibrillation and a presumably noncardioembolic index stroke would be best addressed by a randomized, controlled trial involving this specific patient group. To have a 90\% power to detect a 50\% difference (reduction in recurrent stroke rate from 10\% to 5\%), the trial would require 1100 patients. If the effect of treatment is smaller (reduction from 10\% to 7\%), 3600 patients would be needed. A randomized, controlled study of such a size would present considerable logistical challenges and expense, being larger than any previous investigation of anticoagulation in atrial fibrillation. In addition, it would be unethical to randomize such large numbers of patients to a less optimal treatment on the basis of existing evidence and current recommendations that strongly advocate the use of anticoagulation in all stroke patients with atrial fibrillation if there are no contraindications.

Observational cohort studies may quite often be the only method of identifying significant differences in outcome in clinical practice, especially in situations in which randomization would be unethical or unfeasible. Comparison of study designs has shown that well-conducted nonrandomized trials can yield information similar to randomized trials without putting patients at risk.\textsuperscript{20} These studies can be seen as hypothesis generating and as a robust method for gaining information on patient characteristics, expected size of effect, and logistical constraints that can be used to justify and design targeted randomized, controlled studies. This strategy was used for the present study. In view of existing evidence, all eligible patients were offered anticoagulation as the treatment of choice. The use of aspirin was limited to patients with contraindications to anticoagulation or those who were unable to take warfarin for reasons of choice, compliance, or logistics. Despite being a nonrandomized comparison, the end points of this study were defined in advance; data were collected prospectively; subtyping of stroke was undertaken with appropriate blinded clinical, radiographic, ultrasound, and echocardiographic assessments; and 100\% follow-up was achieved to ensure that the sources of bias were kept to a minimum.

The presence of atrial fibrillation is a major confounding factor in stroke subtype assignment because most patients have a potential embolic source. Recent studies have defined criteria that allow discrimination between embolic and non-embolic stroke\textsuperscript{9,10} that are similar to those used in this study. These studies have shown similar proportions of cardioembolic (68\%) and noncardioembolic strokes in patients with atrial fibrillation and found that warfarin did not reduce noncardioembolic (lacunar and atheroembolic combined) strokes.\textsuperscript{20} It is acknowledged that accurate subtyping of stroke may not be possible in all cases even with advanced neuroimaging and vascular imaging techniques and that some “lacunar” strokes may have cardioembolic or atheroembolic sources.\textsuperscript{21–23} Conversely, because it was not possible to examine the whole arterial system for every patient, some “cardioembolic” strokes may have originated in the aorta or intracranial vessels.\textsuperscript{21} Bias resulting from misclassification was reduced by the use of 2 independent observers and categorizing of patients as undetermined if there were any doubts about source, a strategy used in other similar studies.\textsuperscript{9,10}

Previous primary prevention studies involving atrial fibrillation and stroke have identified secondary variables associated with increased stroke risk.\textsuperscript{1} All patients included in this secondary prevention study were at high risk because of their index strokes. The important clinical uncertainty in the prevention of recurrent stroke is the validity of anticoagulation in lacunar stroke patients who have associated atrial fibrillation. Post hoc analysis by subtype was not undertaken in the only large randomized, controlled study on secondary prevention of stroke in patients with atrial fibrillation.\textsuperscript{2} Although it is possible that patients with lacunar stroke who have atrial fibrillation may benefit from the “primary” preventive effect of warfarin, this remains unproved because of the very small numbers of lacunar stroke in both the placebo and intervention groups in primary prevention studies.\textsuperscript{24,25} One way in which secondary prevention may differ from primary prevention is that stroke recurrence tends to be of the same subtype as the incident stroke.\textsuperscript{26} Patients with lacunar stroke are at a relatively high risk for recurrent stroke, with most of these recurrences being lacunar.\textsuperscript{27} This study suggests that recurrence in patients with lacunar stroke is unaffected by treatment with warfarin despite the wide CIs (because of a relatively small sample size). It is also interesting to note that in the lacunar group, 2 patients suffered intracranial hemorrhage on warfarin and 2 patients treated with aspirin had a cardioembolic stroke, suggesting that the benefits of anticoagulation may be cancelled by the bleeding risk. The higher risk of intracranial bleeding with warfarin in patients with small-vessel cerebrovascular disease has also been reported in the Stroke Prevention in Reversible Ischemia Trial (SPIRIT).\textsuperscript{11}

Although it may be difficult to argue against the use of anticoagulation in patients with cardioembolic strokes, there is genuine uncertainty as to whether patients in atrial fibrillation who have other subtypes of stroke, especially lacunar, benefit to a similar extent. Accurate subtyping of stroke requires clinical expertise and unrestricted, early access to a range of diagnostic facilities,\textsuperscript{28} which requires considerable investment in stroke services.\textsuperscript{29} Similarly, clinical decisions not to anticoagulate a proportion of patients who would be considered eligible according to existing criteria have ethical and legal implications that require hard evidence for support.
Clearly, this issue needs to be investigated further by well-designed trials that are informed by clinical observations such as those reported in this study.

References


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