Secondary Stroke Prevention in Atrial Fibrillation
Lessons From Clinical Practice

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Background and Purpose—Secondary prevention trials do not distinguish outcomes according to stroke cause. The purpose of the study was to determine whether trial efficacy of anticoagulation for secondary prevention could be replicated in clinical practice in strokes of different etiology.

Methods—A 2-year observation study was undertaken in 288 stroke patients with atrial fibrillation (mean age 76 years; 55% women) who were receiving anticoagulation therapy to maintain an international normalized ratio of 2.0 to 3.0. Comparisons were made of (1) patient characteristics, anticoagulation control, and annual stroke/hemorrhage rates with those of the European Atrial Fibrillation Trial and (2) cause of recurrent stroke by initial stroke subtype.

Results—Subjects were 5 years older (95% CI 3 to 7 years), and more patients had small-vessel stroke (26% versus 14%; 95% CI 3% to 17%) compared with corresponding trial data. The duration spent in the target anticoagulation range (55% versus 59%), recurrent stroke rate (5.1% versus 3.6% per year), and major (2.3% versus 2.2% per year) or minor (9.5% versus 11.8% per year) hemorrhage rates were comparable with those in patients receiving warfarin in the randomized study. Ten of 14 (71%) of embolic recurrences occurred in patients with a previous cardioembolic episode, and 8 of 11 (73%) lacunar recurrences occurred in patients with previous lacunar stroke as the qualifying event for anticoagulation ($P=0.025$). Only 3 of 14 cardioembolic compared with 8 of 11 lacunar recurrences occurred during adequate anticoagulation.

Conclusions—Anticoagulation for secondary stroke prevention in clinical practice achieves outcomes comparable with those of randomized trials. Nearly 26% of qualifying strokes and 40% of recurrences were nonembolic; stroke subtype should be considered when making treatment decisions. **(*Stroke*. 2000;32:2106-2111.)**

Key Words: anticoagulation ■ atrial fibrillation ■ secondary prevention ■ stroke subtypes

Patients with nonrheumatic atrial fibrillation and a recent, nondisabling stroke have a high risk of stroke recurrence of approximately 12% per year.[1] Anticoagulation has been shown to reduce this risk significantly, but much of the evidence is based on primary prevention studies.[2] There is only 1 study in secondary prevention, the European Atrial Fibrillation Trial (EAFT), which has shown an absolute risk reduction of 8.4% per year with anticoagulation in patients with transient ischemic attacks or minor strokes.[3]

There is a paucity of evidence that anticoagulation of stroke patients in atrial fibrillation will have similar effects on recurrence in clinical practice. Patients in the trial may not be representative of clinical practice because of selection bias favoring younger or fitter subjects.[4] Of the 1007 patients recruited from 108 centers, only 225 were allocated to anticoagulation (an average of 2 patients per center), and a significant proportion (12%) did not have lesions on CT scans.[3] Not all strokes in patients with atrial fibrillation are cardioembolic; nearly a third of the patients in atrial fibrillation suffer atherosclerotic or small-vessel strokes.[5,6] This is particularly important in the age group with a higher prevalence of atrial fibrillation, because increasing age has also been associated with higher levels of small-vessel disease.[7] Anticoagulation may not prevent a recurrence and may even increase the risk of intracranial hemorrhage in these patients.[8] Previous clinical trials have made little attempt to distinguish stroke outcomes according to cause, and there is a possibility that anticoagulation may have a differential effect depending on stroke subtype.[9]

Identifying the cause of stroke may have implications for the decisions on long-term anticoagulation in stroke patients with atrial fibrillation. The objectives of this prospective cohort study were to compare the outcome of secondary prevention in clinical practice with trial data and to assess the influence of the subtype of the qualifying stroke on recurrence in anticoagulated stroke patients.

Subjects and Methods

Setting and Subjects

A prospective cohort study was undertaken in ischemic stroke patients with atrial fibrillation admitted to a district general hospital

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in southeastern England between January 1994 and December 1997. Inclusion criteria were age <90 years, stroke severity grade of 3 or less on the modified Rankin scale,[10] electrocardiographically proven atrial fibrillation, echocardiographic evidence of atrial dimension >2.5cm/m^2, focal left ventricular wall movement abnormalities, cardiomyopathy (global dyskinesia with a left ventricular ejection fraction <40%), or intracardiac thrombus.[11] Exclusion criteria were a history of bleeding from the gastrointestinal or genitourinary tract in the 6 months before presentation, known coagulation defects, thrombocytopenia or platelet dysfunction, prior hemorrhagic stroke, excessive alcohol intake, dementia, recurrent falls, and poor drug or clinic compliance.[12] Patients on warfarin at the time of stroke, with poorly controlled hypertension (>180 mm Hg systolic and >110 mm Hg diastolic), who were unwilling to consent to long-term anticoagulation, or who were using nonsteroidal anti-inflammatory drugs regularly were also excluded. The study was approved by the local ethics committee (AJS/SGS/017/94).

Initial assessments included a standardized history and examination, laboratory tests, electrocardiogram, CT scan, carotid duplex ultrasonography, and echocardiography. Ischemic strokes were classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) subtype classification system.[13] A cardioembolic cause was assigned to patients with known cardiac disease, evidence of previous cerebral ischemia in different vascular territories, left atrial enlargement or dyskinetic myocardial segments on echocardiography, and <50% stenosis in the relevant carotid artery. Small-artery occlusion was considered to be the cause of stroke in patients with clinical lacunar syndromes, deep oval white matter or basal ganglia infarcts <1.5 cm and/or periventricular hypodensities on CT scans, and the absence of significant carotid or cardiac disease, despite coexisting atrial fibrillation. Patients with cortical syndromes, infarcts >1.5 cm in diameter on CT scans, and evidence of atherosclerotic internal carotid artery disease (>50% stenosis or heterogeneous plaque) who fulfilled the criteria of atherosclerotic stroke were assigned to the "undetermined" category because a cardioembolic etiology could not be excluded with certainty in the presence of atrial fibrillation. The undetermined category also included patients who had clinical lacunar strokes but had inconsistent CT scan findings, significant carotid disease, or cardiac abnormalities.

All strokes were categorized at 2 levels: by the admitting stroke team and by an independent expert on the basis of masked clinical details and investigations. Independent agreement was seen in 249 (86%) patients (κ=0.78). A consensus was reached in 28 patients; the remaining 11 patients were assigned to the undetermined group.

Anticoagulation Practice

Eligible patients received anticoagulants on the basis of local guidelines for this treatment. Patients with mild to moderate neurological deficits and CT scan lesions of <2.5 cm were given anticoagulants within 72 hours of stroke onset.[14] Anticoagulation was deferred by 2 weeks in patients with larger infarcts.[14] All patients were informed about stroke risk and warfarin use. The target range for anticoagulation was defined as an international normalized ratio (INR) of 2.0 to 3.0 by using adjusted-dose warfarin.[15] The first 4 weeks of anticoagulation were considered to be the induction period, during which the INR was stabilized within the target range. The INR levels during this period were not included in the analysis.

Patients attended the general anticoagulation clinic and were advised about the dose of warfarin on the basis of their INR results by hospital staff who did not see the patients and who were unaware of their participation in the study. The frequency of blood tests and dose adjustment was at the discretion of the anticoagulation clinic, but the duration between blood tests and their results were recorded. The number of days when INR was in the target range was calculated by adding the number of days after the measurement of ratios between 2.0 and 3.0 and a subsequent value out of this range. Patients who discontinued warfarin treatment for >4 weeks were treated as withdrawals, but their data were included in the analysis.

Follow-Up

All patients were followed up for 2 years from the time of stabilization of their INR in the target range. Patients were reviewed every 6 months by a researcher who was unaware of their INR values or their withdrawal from anticoagulation therapy. An assessment was undertaken for neurological symptoms and signs, episodes of bleeding, and illness or changes in medication that might influence anticoagulation control. Hospital records were consulted to document admissions or events that may not have been recalled by the patient. In addition, the patients' family doctors were contacted for any information that may not have been obtained through these sources. Patients who had defaulted from clinic attendance were contacted on the telephone and visited at home by the research team. This strategy enabled 100% completion of all follow-up assessments.

End Points and Statistical Analyses

Ischemic stroke was used as the primary outcome of interest. The World Health Organization definition was used,[16] and a CT scan was undertaken to exclude other pathology. Recurrent strokes were classified for subtype by the TOAST criteria.[13] The classification of stroke subtypes was validated by an independent observer not involved in the original assessments. Agreement on stroke subtype was seen in 28 (80%) of the 35 patients (κ=0.74). Recurrent-stroke patients were assessed for outcome at 3 months by their modified Rankin scale score (5 or 6, severe disability or death; 3 or 4, moderate disability; and 0, 1, or 2, none to mild disability). Intracerebral hemorrhages were counted separately.

All deaths were recorded and a cause assigned on the basis of available clinical information. Deaths due to 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 bleeding episodes were classified as minor.

Baseline variables were presented as mean, median, or proportion as appropriate. Two-sample CIs for the difference of means and proportions were used to compare important prognostic variables between anticoagulated patients in the EAFT[3] and the current sample. The differences were assessed by using Tukey's correction. It was considered important to base the significance of differences on CIs rather than on probability values alone. The event rate per patient-year was calculated, and the exact Poisson CIs were used for comparisons of clinical outcomes because of small numbers (due to a low incidence) in these groups. Subgroup analysis of recurrent stroke in different stroke subtypes was undertaken by the χ^2 test.

Results

Patient Characteristics

A total of 2153 stroke survivors were screened within 1 week of stroke onset. Atrial fibrillation was present in 419 (19%) patients. Of these, 49 (12%) patients were excluded because of a modified Rankin scale score >3 at 2 weeks after stroke, 69 (17%) had contraindications to anticoagulation, and 13 (3%) refused anticoagulation. The remaining 288 (69%) patients were included in the study.

The mean age of patients in the study was 76 years and 55% were women (Table 1). A significantly higher proportion of patients in the clinical sample were >70 years of age and were 5 years older, on average, than those in the EAFT. There were no significant differences in the prevalence of risk factors such as hypertension, diabetes mellitus, smoking, and previous cerebrovascular events between the clinical sample and trial patients. The frequency of cardiovascular disease was significantly higher in the clinical sample, suggesting that these patients had a greater atherosclerotic disease load than did the trial patients. Although the majority of strokes could be attributed to a cardioembolic etiology, a significant

TABLE 1. Clinical Characteristics of Patients in the Clinical Study Compared With EAFT Data for Patients Receiving Warfarin

Variable	Clinical Practice (n=288)	EAFT[3] (n=225)	Difference (95% CI)
Mean age, y (SD)	76 (12)	71 (7)	5 (3.4 to 6.6)*
Age <70 y, n	66 (23%)	37%	14% (6% to 22%)*
Male sex, n	138 (48%)	55%	7% (−2–16%)
Hypertension, n	132 (46%)	43%	3% (−6–12%)
Diabetes mellitus, n	37 (13%)	12%	1% (−5–7%)
Current smokers, n	46 (16%)	19%	3% (−4–10%)
Stroke/TIA in past year, n	49 (17%)	19%	2% (−5–9%)
Congestive heart failure, n	98 (34%)	18%	16% (11–23%)*
Ischemic heart disease, n	81 (28%)	18%	10% (3–17%)*
Clinical stroke subtype			
Cardioembolic, n	161 (56%)	...	...
Undetermined, n	51 (18%)	...	...
Lacunar (white matter), n	76 (26%)	14%	10% (3–17%)*
Median duration of follow-up, y	2.1	2.3	...

TIA indicates transient ischemic attack. Values are number of persons or events in that category, unless indicated otherwise.

*Significant values ($P \leq 0.05$).

proportion of presenting strokes in actual practice were lacunar and due to small-vessel disease (Table 1).

Quality of Anticoagulation

Treatment with warfarin was stopped in 74 (26%) study patients during the follow-up period (Table 2). Although the overall proportion of patients stopping warfarin was comparable with that in the EAFT, significantly more patients stopped treatment because of choice (n=9), compliance (n=7), and logistical problems (n=21) associated with anticoagulation. The proportion of patients stopping treatment as a result of bleeding complications was similar to that in the randomized trial.

Patients in the study sample had their INR in the target range for an average 55% of the time (range 29% to 74%), below target for 26% of the time (range 12% to 34%), and above target for 19% of the time (range 7% to 29%) (Table 2). An INR >5.0 (when risk of bleeding is greatest) was present 4% of the time. There were no significant differences in the proportion of time spent in the target range between patients over and under 70 years of age. The time spent in the target range in clinical practice was comparable to that in the EAFT (a difference of 4%; 95% CI −6% to 14%). However, patients in the clinical sample spent significantly more time above the target range. This result may have occurred because of the narrower target range (INR of 2.0 to 3.0) recommended for clinical practice compared with that in the randomized trial.[15]

End Points

All surviving patients were followed up for the planned duration regardless of withdrawal from anticoagulation. There were 32 ischemic strokes in the study sample, 9 of which were fatal (Table 3). Fourteen of these were judged to be definitely cardioembolic, 7 were indeterminate (atherosclerotic or cardioembolic etiology equally likely), and 11were due to small-vessel disease (Table 4). Ten of the 14 (71%) embolic recurrences occurred in patients who had initially presented with a cardioembolic stroke, and 8 of the 11 (73%) lacunar recurrences occurred in patients in whom a lacunar stroke had been the qualifying event for anticoagulation (Table 4). These differences were statistically significant ($P=0.025$).

Of the 32 ischemic strokes in the study, 16 occurred in patients on warfarin treatment (annual stroke rate 3.8%; 95% CI 2.0% to 5.6%) and 16 in patients from whom warfarin had been withdrawn (annual stroke rate 8.5%; 95% CI 4.3% to 12.7%). Only 3 of the 14 cardioembolic recurrences occurred during adequate anticoagulation (INR range of 2.3 to 2.8). In contrast, 8 of the 11 patients with lacunar strokes were adequately anticoagulated at the time of recurrence (INR of 2.1 to 3.5). Embolic recurrences were more common in the

TABLE 2. Anticoagulation Practice and Quality of Control

Characteristic	Clinical Practice	EAFT[3]	Difference (95% CI)
No. of patients	288	225	...
No. of patients stopping warfarin	74 (26%)	48 (21%)	5% (−2–12%)
Reasons for withdrawal			
Bleeding complications	25 (9%)	18 (8%)	1% (−4–6%)
Choice/compliance/logistics	37 (13%)	16 (7%)	6% (1–11%)†
Other	12 (4%)	14 (6%)	2% (−2–6%)
Quality of control*			
Target INR range	2.0–3.0	2.5–4.0	...
Target INR value	2.5	3.0	...
Mean INR value (SD)	2.4 (0.8)	2.9 (0.7)	...
Time spent in target range	55%	59%	4% (−6–14%)
Time below target range	26%	32%	6% (−2–14%)
Time above target range	19%	9%	10% (4–16%)†

*After an initial period of stabilization of INR values.

†Significant values ($P \leq 0.05$).

TABLE 3. Clinical Events in Patients on Warfarin

	Clinical Practice (612 Patient-Years)*		EAFT (507 Patient-Years)*		
	No. of Events	Annual Event Rate (95% CI)	No. of Events	Annual Event Rate (95% CI)	Rate Ratio (95% CI)
All strokes	35	5.7% (3.8–7.6%)	20	3.9% (2.2–5.6%)	1.46 (0.79–2.61)
Ischemic stroke (IS)	32	5.1% (2.3–7.0%)	18	3.6% (1.9–5.3%)	1.43 (0.74–2.36)
Fatal/major disability†	9		6		
IS with moderate disability†	11		4		
IS with no/mild disability†	12		8		
Intracranial hemorrhage (ICH)	3	0.5% (0.2–0.8%)	2	0.4% (0.05–0.75%)	1.25 (0.14–15.7)
Mortality (excluding stroke)	36	5.9% (4.0–7.8%)	31	6.1% (4.0–8.2%)	0.96 (0.58–1.61)
Vascular deaths	22	3.6% (2.1–5.1%)	20	3.9% (2.2–5.6%)	0.92 (0.45–1.54)
Cardiac	14		14		
Noncerebral bleeds	3		3		
Other vascular causes	5		3		
Nonvascular deaths	14	2.3% (1.1–3.4%)	11	2.2% (0.9–3.5%)	1.05 (0.45–2.63)
Bleeding events	58	9.5% (7.1–11.9%)	60	11.8% (8.8–14.8%)	0.80 (0.45–1.35)
Major (excluding ICH)‡	15	2.5% (1.2–3.8%)	13	2.6% (1.2–4.0%)	0.96 (0.41–2.13)
Minor	43	7.0% (4.9–9.1%)	47	9.2% (6.6–11.8%)	0.76 (0.41–1.47)

*Patient-years given for stroke and transient ischemic attack; patient-year exposures for others are variable.
†Functional deficit assessed 3 months after the event (variably measured in different studies).
‡Bleeding complications requiring admission or transfusion were classified as major, for consistency with other studies.

first year (10 of 14), whereas nonembolic recurrences were distributed evenly over the period of follow-up.

Three patients suffered an intracranial hemorrhage at 3, 12, and 17 months after commencing warfarin. The INRs at the time of admission were 2.8, 5.2, and 6.9, respectively. All 3 patients had INR ratios within the target ranges on a prior test, and there was no history of illness or change in medication. Thirty-six patients died of noncerebral causes during the period of observation (Table 3). Twenty-two of these deaths were vascular, the majority being due to cardiac causes.

Three patients died due to major gastrointestinal bleeding from a previously undiagnosed pathological condition (colorectal carcinoma, bleeding peptic ulcer, and angiodysplasia in 1 each). There were 12 other major bleeding events, mostly in the gastrointestinal tract. Minor bleeding episodes were seen in 43 patients and included epistaxis (n=12), hemoptysis (n=4), bruising (n=7), rectal bleeding (n=7), hematuria (n=9), and bleeding gastric erosions (n=4). Warfarin was stopped temporarily in these patients (<4 weeks). Twenty-one patients had INRs >5.0 (range 5.1 to 9.7) without suffering any bleeding complications and were returned to the target range by adjustment of their warfarin dose.

The ischemic stroke incidence rate of the study group (5.2% per year; 95% CI 3.4% to 7.0% per year) was comparable with that of patients in the warfarin group of the EAFT (3.6% per year; 95% CI 1.9% to 5.3% per year). The incidence of intracranial hemorrhage and mortality due to any reason were comparable between the clinical sample and the randomized trial data (Table 3). The frequency of major bleeding complications in actual practice (2.5% per year; 95% CI 1.2% to 3.8% per year) was also not significantly different from that seen in the EAFT (2.6% per year; 95% CI 1.2% to 4.0% per year). Although the annual stroke rate in anticoagulated lacunar stroke patients was nearly twice that of anticoagulated cardioembolic stroke patients, this difference did not achieve statistical significance (P=0.067).

Discussion

Stroke patients in clinical practice were older and had higher levels of comorbidity compared with trial patients.

TABLE 4. Subgroup Analysis of Recurrent Stroke in Patients on Warfarin in the Study According to TOAST Criteria

Stroke Subtype	No. of Patients	No. of Patient-Years	No. of Strokes	Event Rate (95% CI)	Cardioembolic	Undetermined	Lacunar	Bleed
Cardioembolic	161	346	16 (5)	4.6% (2.3–6.9%)	10 (3)	4 (2)	1	1
Undetermined	51	102	5 (2)	4.9% (3.1–6.7%)	2 (1)	1 (1)	2	0
Lacunar	76	164	14 (2)	8.5% (4.0–13.0%)	2 (1)	2	8 (1)	2
Total	288	612	35 (9)	5.7% (3.8–7.6%)	14 (5)	7 (3)	11 (1)	3

Numbers in parentheses denote patients with disabling ischemic stroke in each subtype.

Despite these differences, the overall stroke rate, mortality, and the hemorrhage rate were comparable with those in the randomized study, suggesting that the efficacy of anticoagulation in secondary prevention translates into clinical practice. The study also showed that a significant proportion of patients in clinical practice presented with lacunar (small-vessel) stroke, even in the presence of atrial fibrillation. The recurrent stroke rate in these patients was twice that of cardioembolic stroke despite their being on anticoagulation therapy, and the majority of recurrences were of small-vessel (lacunar) origin.

The current study is representative of actual practice and includes patients who would be considered for such management. It was undertaken in a district general hospital, and an incident stroke register was used to prevent selection bias. This procedure was reflected in the older age group of patients included in the study and the higher levels of disease affecting other sites, including the heart and the small, penetrating arteries of the brain. Similar differences between trial subjects and actual practice have been seen in primary prevention studies.[17,18]

The risk of altering anticoagulation practice to favor intervention was kept to a minimum by using general clinics, which managed these patients as part of their routine work load and were unaware of their participation in the study. A prospective design was used to ensure that all withdrawals, anticoagulation deviations, events, and complications were identified. Recall bias for events, especially minor bleeding episodes, was prevented by not only depending on the patients' memory for such events during structured interviews but also reviewing hospital records and information from general practice sources. Preference bias for stroke subtype of recurrent events was reduced by corroboration with an independent observer who was masked to previous assessments and anticoagulation status.

The ischemic stroke rate seen in clinical practice was 42% higher (5.1% versus 3.6% per year) than that in EAFT, raising the possibility of a type II error. This stroke rate lies within the 95% CI of the EAFT (1.9% to 5.3% per year), suggesting that it would be difficult to show a significant difference at the 5% level, even with an unrealistically large sample. In addition, the stroke rate for patients actually receiving therapeutic anticoagulation was 3.7%, which approximates the rates seen in the EAFT.

Only 50% of the original 419 stroke patients with atrial fibrillation were anticoagulated for the entire duration of the study. A third of the patients in actual practice had severe strokes or contraindications to anticoagulation, and warfarin was discontinued in another 74 patients (18%) for various reasons. Although the proportion of withdrawals was similar to that of the randomized study, more patients in actual practice stopped treatment because of nonclinical reasons. It may not be possible to undertake anticoagulation in older people despite their being eligible on the basis of clinical criteria because of mobility problems, sensory impairments, use of other drugs, mood disorders, health behavior, and access to anticoagulation services. The impact of these factors on prevention strategies has not been researched. These patients, in whom the intention was to treat, were included in the analysis because the "true effectiveness" of anticoagulation in actual practice needs to reflect outcome in this group as well as in "treated" patients.[19]

Ischemic strokes occur in patients with nonrheumatic atrial fibrillation for a variety of reasons and not exclusively due to cardiogenic emboli.[5,6,9] This finding was seen in this study, wherein nearly a quarter of the patients admitted with stroke and atrial fibrillation had strokes due to small-vessel disease. The recurrence rate in these patients was high and most of the recurrences were not cardioembolic, despite the presence of atrial fibrillation. Existing criteria for anticoagulation in atrial fibrillation do not distinguish between different stroke subtypes and would not preclude these patients from long-term anticoagulation.[20–22] Anticoagulation in patients with small-vessel cerebrovascular disease may be associated with an increased risk of intracranial bleeding,[8] and any benefit of preventing cardioembolic stroke may be offset by the increased risk of intracranial hemorrhage. It is possible that aspirin alone or in combination with warfarin may be a better preventive measure in these patients.

There is no doubt that anticoagulation is effective in preventing recurrence in the majority of stroke patients with atrial fibrillation and that these benefits are replicated in clinical practice. However, anticoagulation may have a differential effect according to stroke mechanism, regardless of the presence of atrial fibrillation. Although the clinical criteria for etiological subtyping of stroke are imperfect and some cardioembolic strokes may be misclassified as lacunar events, the current study emphasizes the importance of careful consideration of the cause of stroke before initiating measures to prevent recurrence.[23]

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