Risk of Recurrent Stroke in Patients with Atrial Fibrillation and Non-Valvular Heart Disease

JACOB I. SAGE, M.D.,* AND ROBERT L. VAN UITERT, M.D.†

SUMMARY One-hundred-forty patients with atrial fibrillation (AF) due to non-rheumatic, non-valvular heart disease (NVHD) who suffered a cerebral infarct were identified. Fifty-three (38%) died of the initial stroke. The surviving patients were followed up to 9 years without anticoagulant therapy. In the 59 patients available for follow-up, the risk of recurrent cerebral ischemia remained at approximately 20% per year throughout the 9 year observation period. The recurrence rate was the same regardless of age, sex, previous myocardial infarction, or whether chronic AF or intermittent AF were present. Only 7 (12%) died from a second stroke, however. The high annual rate of recurrence and lack of controlled therapeutic trials in this population of patients warrant a prospective study to define the benefits and relative risks of anticoagulant therapy in AF due to NVHD.

STROKE OCCURS FIVE TIMES more frequently in patients with atrial fibrillation (AF) than in the general population.¹ Cerebral embolism from a cardiac source accounts for most of the increased risk of stroke in these patients. Although the use of anticoagulants to prevent recurrent cerebral emboli in patients with cardiac disease now has gained general acceptance, conflicting data continue to fuel the debate over the timing of initiation of treatment, length of time to maintain therapy, and whether anticoagulants should be used in all or in selected members of this population.²,³

Most studies supporting anticoagulant therapy have not considered that the risk of re-embolization may vary with the type of cardiac disease underlying the AF.⁴-⁹ Differing therapeutic recommendations may in part reflect differences in the natural histories of the various causes of emboli. A uniform approach to treatment of cerebral embolism from all cardiac sources may not exist. Rational treatment strategies must focus on the relative risk of recurrent stroke from each specific cause of embolism.

The natural history of cerebral infarction in patients with AF was documented initially in an era in which most AF was due to rheumatic valvular heart disease (RHD).¹⁰-¹⁵ Studies demonstrating the benefit of anticoagulants in AF also are dominated by patients with RHD.⁸,¹² More recently, the incidence of RHD has declined; now, AF most commonly occurs from non-rheumatic non-valvular heart disease (NVHD), presumably due to coronary atherosclerosis and atrial ischemia.¹⁶ The present report examines the natural history of a large population of patients presenting with stroke and AF due to NVHD who were followed for up to nine years without anticoagulant therapy.

Methods
We reviewed the records of all patients from Middlesex General Hospital, New Brunswick, New Jersey, for the years 1970 through 1980 who had a diagnosis suggesting cerebral infarction. Patients accepted into the study group had a sudden stepwise or fluctuating focal neurological deficit, maximal at or shortly after onset, which persisted for at least 24 hours. All study patients had electrocardiographic (ECG) evidence of atrial fibrillation without a history or clinical evidence of rheumatic heart disease. Nonvalvular heart disease was inferred from the lack of cardiac murmurs or clicks on examination and the absence of annulus or valvular calcification on chest x-ray. Echocardiography was not routinely performed. Five patients with angiographically demonstrated carotid atheromatous disease were excluded from the study.

Follow-up information on patients was obtained by personal communication and examination of the patient by one of us (J.S.) or, in the event of death, from subsequent medical records and contact with the patient’s closest surviving relatives. Recurrent stroke, degree of disability both before and after recurrent stroke, and causes of death were identified. Patients were graded for degree of disability as described in Table 1. A functional status change by two or more levels was considered significant.

As was customary at Middlesex General Hospital during the period of this study, none of the study patients received anticoagulant therapy either during or subsequent to their initial hospitalization for cerebral infarction. No patients had to be excluded from the study because of anticoagulant use.

Results
One-hundred-forty patients were identified who suffered from stroke associated with AF and NVHD. Women outnumbered men 83 to 57. Cerebral infarction occurred in the left carotid distribution in 56 patients, in the right carotid distribution in 61, in both anterior circulations in 5 patients and in the vertebrobasilar system in 18. In 35 patients (25%), AF was intermittent and alternated with normal sinus rhythm on repeated ECG examinations during the patient’s initial hospitalization. AF was chronic and persistent on all ECG’s throughout the entire study period in the other 105 patients.

Most study patients had evidence of myocardial
Twenty-two patients (37%) had thirty-one subsequent cerebral ischemic events. Seven patients died of recurrent stroke (32% of patients with recurrent stroke, but only 12% of the 59 followed survivors), i.e., 23% of recurrent emboli were fatal. Twenty patients succumbed to cardiac disease, 4 died of pneumonia and one each died of a ruptured aortic aneurysm, subdural hematoma, and of post-operative complications from a femoral-popliteal bypass.

Table 2 details the time-dependant risk of recurrent cerebral infarction in the 59 follow-up patients. The risk of recurrent stroke remained at approximately 20% per year throughout the 9 year follow-up period. No significant difference (p > 0.05) was apparent in the annual stroke recurrence rates between groups of patients who had ECG evidence of myocardial infarction, those who had diabetes mellitus or hypertension, and patients without these signs or risk factors for atherosclerotic heart disease.

Age and sex do not seem to play major roles in determining the risk or outcome of recurrent stroke. There was no significant difference (p > 0.05) between the age of those patients who remained alive without recurrences (70.5 ± 8.7 years), those who survived both the initial infarct and recurrent stroke (75.6 ± 9.8 years), or those who died of recurrent cerebral infarction (73.6 ± 5.4 years). Similarly, there was no significant difference in outcome among women and men in the follow-up group (p > 0.05). Thirty-three women and 26 men were followed. Among this group, 20 women and 17 men had no recurrent emboli during the follow-up period. Eleven women had 16 recurrences which they survived. Six men suffered 8 recurrences which they survived. Two women and 3 men died of the first recurrence. One woman and one man died of a recurrence subsequent to the first.

The chance of recurrent stroke was no greater in patients with intermittent AF than in those with chronic persistent AF. Thirty-seven percent (13/35) of patients with intermittent AF and 38% (40/105) with chronic AF died of the original embolus. Of survivors available for follow-up 36% (4/11) of patients with intermittent AF and 37% (18/48) with chronic AF had recurrent emboli.

The arterial territory involved by the original embolus had no bearing on the frequency of recurrent events. Eighteen of the original 140 patients (12.9%) had posterior circulation strokes. Seven of 53 patients

**TABLE 1 Grades of Disability**

<table>
<thead>
<tr>
<th>Grade Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No functional loss, may have mild hemiparesis only</td>
<td>1</td>
</tr>
<tr>
<td>Moderate hemiparesis or aphasia, no aid necessary</td>
<td>2</td>
</tr>
<tr>
<td>Severe hemiparesis — walks with aid</td>
<td>3</td>
</tr>
<tr>
<td>Severe hemiparesis — only activities of daily living with aid</td>
<td>4</td>
</tr>
<tr>
<td>Severe hemiparesis — cannot do activities of daily living</td>
<td>5</td>
</tr>
<tr>
<td>Severe hemiparesis — full nursing care</td>
<td>6</td>
</tr>
<tr>
<td>Depressed level of consciousness with hemiparesis</td>
<td>7</td>
</tr>
<tr>
<td>Unresponsive</td>
<td>8</td>
</tr>
</tbody>
</table>

ischemia or risk factors for ischemic heart disease. Fifteen patients had overt diabetes mellitus, 29 chemical diabetes, and 33 were hypertensive. Thirty-three patients had ECG evidence of remote myocardial infarction, though a clinically apparent infarct had occurred only in 16. No patients had angina without ECG evidence of infarction, hyperthyroidism, amyloidosis or cardiomyopathy.

Eighty-nine of the 140 patients had systemic emboli or angiographic, CT, or autopsy evidence consistent with an embolic origin of cerebral infarction. Limb emboli occurred in 18 patients either prior to or after cerebral infarction. Cerebral arteriography, performed in 3 patients, demonstrated cut-off distal vessels. A CT scan was obtained in 14 patients and revealed one or more areas of lucency in peripheral cortical distributions. The 9 patients on whom autopsies were performed all had one or more infarctions near the surface of the cerebral cortex, although a cardiac thrombus was found in only one patient at post-mortem. Fifty-seven patients (41%) had transient microscopic hematuria at the time of the initial stroke suggesting coincident renal micro-emboli; three had renal infarcts at autopsy (33% of autopsied patients). Of fifty patients suffering from stroke not associated with AF who were contemporaries of the study patients, only 2 (4%) had transient microscopic hematuria.

Death occurred either from the initial infarct or its complications in 53 patients (38%). Of the 87 survivors, accurate follow-up information was obtained in 59 with a mean follow-up period of 3.1 ± 2.3 years. Twenty-two patients (37%) had thirty-one subsequent cerebral ischemic events. Seven patients died of recurrent stroke (32% of patients with recurrent stroke, but only 12% of the 59 followed survivors), i.e., 23% of recurrent emboli were fatal. Twenty patients succumbed to cardiac disease, 4 died of pneumonia and one each died of a ruptured aortic aneurysm, subdural hematoma, and of post-operative complications from a femoral-popliteal bypass.

**TABLE 2 Time of Recurrent Stroke After Initial Embolus**

<table>
<thead>
<tr>
<th>Years after initial embolus</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>59</td>
<td>58</td>
<td>55</td>
<td>42</td>
<td>28</td>
<td>20</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Remaining in follow-up group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent emboli not causing</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death from recurrent emboli</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Percent recurrences of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>population still at risk</td>
<td>17%</td>
<td>14%</td>
<td>25%</td>
<td>10%</td>
<td>25%</td>
<td>25%</td>
<td>66%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The arterial territory involved by the original embolus had no bearing on the frequency of recurrent events. Eighteen of the original 140 patients (12.9%) had posterior circulation strokes. Seven of 53 patients
(13.2%) who died of the original embolus had posterior or circulation events. Within the 59 patients in the follow-up group, 3 of 7 patients with vertebral-basilar emboli (43%) and 19 of 52 patients with carotid events (37%) had recurrences.

Three of 24 non-fatal recurrent episodes of stroke caused significantly increased functional disability. The degree of patient disability at the time of discharge from the hospital following one episode of cerebral infarction, however, had no bearing on the outcome or occurrence of subsequent stroke. There was no significant difference ($p > 0.05$) in the functional status between those who had no subsequent stroke (Table 1 disability grade $2.3 \pm 2.4$), those who survived subsequent stroke ($3.0 \pm 1.9$), and those who died of recurrent cerebral infarction ($3.2 \pm 2.6$).

**Discussion**

The usual mechanism of arterial occlusion in patients with AF who suffer a cerebral infarct is assumed to be an embolus of atrial origin. Proof that a cerebral infarct is caused by cardiogenic emboli is frequently difficult to obtain even at autopsy, however. The clinician confronted with a patient suffering from AF and stroke often must infer embolism from the clinical setting without proof. The present study describes the natural history of a population of patients with the common clinical presentation of stroke associated with AF of non-rheumatic, non-valvular origin. Though the presentation in all study patients was consistent with embolic infarction, definitive proof of cardiogenic emboli was unobtainable in most patients. While the present evidence does not absolutely rule out a heterogeneous cause for emboli and stroke, the study is directed toward the uniform clinical presentation of stroke associated with AF and NVHD and results should be applicable to this clinical setting.

Recurrent cerebral embolism associated with AF previously has been studied mostly in patients with rheumatic valvular heart disease. Easton and Sherman reviewed the available data and found an overall embolic recurrence rate ranging from 30 to 75% in this population. Because of differing methods of performance and reporting, further detailed cumulative information is difficult to extract from the published studies. In five studies of RHD in which the reported data does allow pooling of information, 5–8, 10 36% of 367 patients with RHD (75% with AF) suffered recurrent cerebral emboli when followed up to 12 years. Thirty-three to 55% of emboli occurred within 6 months of an initial embolic infarct, and an additional 12 to 17% occurred in the next 6 months. Mortality due to recurrent stroke in all survivors of the initial infarct was approximately 30%.

The eventual risk of recurrent stroke in patients with AF and NVHD is the same as in patients with RHD, but the time of re-embolization differs considerably. Thirty-seven per cent of the survivors of the initial embolus in the present study sustained a second stroke within 9 years; this risk of recurrent embolus is virtually identical with the 36% chance of recurrence in the combined RHD population. In an autopsy study, Hinton, et al. also found the overall incidence of emboli to be similar in patients with AF and NVHD and with RHD. Most repeated emboli associated with RHD, however, occur within the first year after an initial infarct. In contrast, the present study demonstrates that the risk of recurrent emboli in patients with AF and NVHD is only 17% in the first year but remains at or above this level for at least the subsequent nine years (Table 2). The work of Wolf, et al. supports this finding; they noted only 5 of 20 cerebral emboli occurred within 1 year after onset of new AF in patients with NVHD who had not sustained a previous infarct, and the remaining 15 emboli were scattered over the subsequent 15 years of follow-up. Bharucha, et al. have recently reported in abstract that 7% of patients with NVHD suffer stroke within one year of onset of new AF, whereas 14% of patients with RHD and AF sustain a cerebral infarct in the same time period. Although the patient with NVHD has a lesser chance of suffering a cerebral infarct than the patient with RHD in the first year after an initial embolus, the equal long-term morbidity from recurrent emboli in the 2 populations implies that the NVHD patient’s risk of re-embolization rises above that of the RHD patient in subsequent years.

Most patients with AF and NVHD die of causes other than recurrent stroke. Twenty-seven of 59 survivors of the initial embolus (46%) succumbed during the follow-up period to illnesses other than cerebral infarction. As has been found in other studies of stroke in patients with arteriosclerotic cardiovascular disease, the most common cause of death in the present population was cardiac disease. Only 12% of the patients died of recurrent stroke compared with 30% of patients in the combined RHD studies, even though the risk of recurrence in each group is the same. The higher mortality in RHD may reflect the fact that most studies of RHD occurred over 20 years ago when the management of stroke and serious cardiac disease was less advanced. As only 13% of recurrent non-fatal emboli in NVHD caused significantly increased disability, however, an alternative explanation may be that many emboli in patients with NVHD are small and cause mild or transient deficits.

Paroxysmal AF did not cause a higher incidence of recurrent stroke than did chronic persistent AF, nor did it predispose to a higher mortality from stroke. In both groups, approximately 37% of patients died of their initial infarct and approximately 37% of survivors sustained a second stroke within 9 years. Age, sex, arteri- al distribution, previous myocardial infarction, and pre-existing neurologic deficits also did not influence the chance of reembolization or of death when a second stroke did occur.

Since the natural history of stroke due to AF and NVHD differs from that of RHD, studies dominated by the latter cannot serve as a basis on which to determine treatment for the prevention of cerebral ischemia in patients with NVHD. Recent studies in mixed populations of patients with RHD and NVHD have recom-
mended the institution of heparin immediately after an initial infarct\textsuperscript{2-20} to prevent early re-embolization. Recurrent emboli tend to occur early in patients with RHD, but not in NVHD: the earliest recurrence in the present study was 12 days after an initial embolus. The present study suggests that more gradual anticoagulation with oral warfarin may be appropriate in patients with AF due to NVHD. Once beyond the first year after infarction, patients with NVHD and AF remain at substantial risk for recurrent stroke for at least nine years. Ideally, prophylaxis against recurrent emboli should be maintained for at least the same length of time in patients with NVHD. It is not clear, however, that long-term use of oral anticoagulants is the optimal treatment for all such patients. The risk of complications from anticoagulants in a population whose mean age is 72.9 years, and in whom a neurologic deficit already exists, could be substantial and may exceed the chance of recurrent emboli. The high annual rate of recurrence, as well as uncertain benefit from current prophylactic therapy, warrant a prospective study to define the advantages and relative risks of anticoagulation in this subgroup of patients with AF.

Acknowledgment

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