Risk Factors for Stroke and Other Embolic Events in Patients With Nonrheumatic Atrial Fibrillation

Kenneth M. Flegel, MD, MSc, FACP, and James Hanley, PhD

Factors associated with stroke and other cardiac embolic events in subjects with nonrheumatic atrial fibrillation were examined in a retrospective study of 91 patients from a teaching hospital clinic. There were 28 first strokes during 355 person-years of follow-up (7.9 per 100 person-years). Patients who had experienced one or more previous events were approximately 2.3 times more likely to have a subsequent event (hazard ratio 2.3, 95% confidence interval 1.5–3.4) than patients who had experienced no events. A univariate analysis of factors associated with a first stroke of any cause or other embolic event showed that age of >75 years (hazard ratio 2.5) and systolic blood pressure of >160 mm Hg (hazard ratio 6.4) were significant factors. After adjusting for the effect of age and systolic blood pressure, previous events still carried an increased risk for subsequent events. Subjects with nonrheumatic atrial fibrillation who have had one or more embolic events are at high risk of further emboli. They require special consideration when treatment is being planned. (Stroke 1989;20:1000–1004)

Subjects with nonrheumatic atrial fibrillation (NRAF) are 6–7 times more likely to suffer from a stroke than are age-matched controls without this dysrhythmia.1,2 It is likely that most of the strokes are due to emboli from clot formation in the left atrium.3–5 Anticoagulant therapy could potentially reduce the incidence of such strokes by preventing clot formation, but the added risk of hemorrhage, particularly intracerebral hemorrhage, has made it difficult for clinicians to decide on the best treatment policy.5–6 While a randomized trial of warfarin has shown a modest general benefit to elderly patients, the number of withdrawals because of difficulties with anticoagulation treatment was high.9 If factors for which a strong association with stroke are identified, we could select a subgroup of patients whose experience with embolic events is different from that of the whole population at risk, allowing a better choice of treatment. For example, the Framingham Study10 and others11,12 have reported that if a stroke has already occurred, the risk of recurrence is high. Also, the rate of stroke appears to increase in the first year after the onset of NRAF.12,13 A recent study of patients <60 years of age at the Mayo Clinic14 found that the risk of stroke in the subgroup of patients with “lone” atrial fibrillation (patients without any other cardiovascular disease) was not increased. However, the older Framingham patients with “lone” NRAF did have an increased risk of stroke.15 Other studies have found a higher risk with chronic versus intermittent NRAF13,16 and with systolic hypertension,2–17 but not with hyperthyroidism.18 Studies of left atrial size have shown no increased risk16–17,19 or an increased risk16,20 compared with poorly matched controls.

We used a clinic population to evaluate factors, including blood pressure, left atrial diameter, aspirin use, and previous stroke, for a time-dependent association with future stroke or other embolism. In addition, we obtained the first precise estimate of the risk of recurrent stroke, taking into account the time since the onset of NRAF and previous stroke.

Subjects and Methods

We examined a teaching hospital outpatient population at the Royal Victoria Hospital, a 700-bed hospital in Montreal. The records of all patients who were registered in two group practices of general internal medicine between 1982 and 1986 were screened for the presence of atrial fibrillation (approximately 8,000 patients). Eligible patients had established atrial fibrillation, as interpreted by a cardiologist, from a standard 12-lead electrocardiogram. NRAF was diagnosed if the clinic notes...
stated that there was no evidence (by history, physical examination, or echocardiogram if done) for rheumatic valvular disease. Patients were excluded from the study if the atrial fibrillation was transient or intermittent, if they were being treated with long-term anticoagulants, or if the follow-up from first documentation was <30 days. Chronic NRAF was diagnosed when two electrocardiograms taken >30 days apart showed atrial fibrillation, with no sinus rhythm on subsequent electrocardiograms.

While only patients who attended the clinic after 1982 had a chance to enter the study, time t=0 was set as the first occasion on which atrial fibrillation was documented by electrocardiogram and on which basic history and physical examination information was taken. Demographic, clinical, and laboratory data were obtained from the record at time t=0.

For all quantitative clinical and laboratory measurements, the lowest value in the 3 months prior to the time t=0 visit was used, except for pulse rate, which was recorded after digoxin had been prescribed and the pulse rate appeared to be at baseline. Echocardiographic measurements were taken, when available (49 patients), from the earliest examination after t=0. Atrial fibrillation was considered of new onset if the clinical record indicated that it was a new event and either a previous electrocardiogram showed sinus rhythm or the clinical notes stated explicitly that there was no history of cardiovascular disease.

The subsequent experience of each patient was determined by means of the hospital record or by the office record of the patient's general physician until one of the following occurred: death, permanent anticoagulation, resolution of the atrial fibrillation, or loss to follow-up. Outcome events counted were stroke, transient ischemic attack, or other embolism to the left cardiovascular circulation as diagnosed by a physician in the clinical record. As with other studies of stroke and NRAF, no attempt was made to distinguish embolic strokes from other types as this distinction requires early cerebral angiography. To be sure that one embolic event was clearly separated from the next, an event was accepted as recurrent if it occurred at least 14 days after a previous one.

In the first statistical analysis, we looked for an association between a first outcome event during the study and each of the following factors as measured at entry into the study: age, sex, heart size as reported from the chest x-ray film, the presence of complete left bundle branch block, blood glucose concentration, serum cholesterol concentration, or prescription for aspirin, digoxin, a diuretic, or a beta blocker. We also looked for an association with specific diagnoses such as coronary artery disease, cardiomyopathy, alcoholism, congestive heart failure, and the major diagnostic categories grouped according to the Tabular List of ICD-9-CM. The Cox proportional hazards model was used to test the effect of the level of each factor at entry for an association with the time until the first outcome event. Factors that appeared to be important from this first statistical analysis were reexamined for an association with stroke events only. Subsequently we tested the same factors in patients with new-onset NRAF.

In a second statistical analysis, all outcome events (including recurrent ones) were examined. The number of all previous events was tested as a time-dependent predictor of subsequent events. Important factors from the first analysis were tested again after adjusting for the effect of previous events. We analyzed recurrent events by organizing the data into risk sets as determined by the order in which events occurred after t=0 for the entire study group. We included in the risk set for each event all patients who were at risk for that event at that time. For each such patient, we used the variable "number of events until now in this patient" as a time-dependent covariate. We used the DATA feature of SAS to construct these risk sets and to perform the proportional hazards regression analysis.

**Results**

One hundred eighty-one patients with atrial fibrillation were identified, of whom 33 had the rhythm transiently, 40 had evidence of rheumatic heart disease, 13 were on long-term anticoagulant therapy, and four had been followed for <30 days. These 90 exclusions left 91 eligible patients for whom entry and follow-up information was intensively sought. The source of clinical information was the current hospital record for 79% of the patients and the general physician for the remaining 21%. The median duration of follow-up was 3.9 years (range 1 month to 15 years). Of the 91 patients entered into the study, 18 were given anticoagulants after a first stroke (median follow-up 2.2 years), 14 died, two reverted to sinus rhythm after a long time with NRAF, and 26 were lost to follow-up (after a median of 3.9 years). The main clinical characteristics of the 91 patients are shown in Table 1. The older age of these patients is notable. There were 28 first events, of which 17 were strokes, seven were transient ischemic attacks, and four were other emboli to the systemic circulation. There were 15 recurrent events (four patients had three sequential events), of which 11 were strokes and four were transient ischemic attacks. Both first and recurrent events appeared to be randomly distributed over the follow-up time despite obvious clustering in two patients with three events.

Factors associated with a first event are shown in the first column of Table 2. For each factor, the hazard ratio, a statistical estimate of the relative risk provided by the proportional hazards model, and the 95% confidence interval (CI) are listed. Some effect was apparent for both systolic blood pressure and age when tested as continuous vari-
TABLE 1. Characteristics of 91 Patients With Nonrheumatic Atrial Fibrillation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (range 50–89)</td>
<td>70.9±8.8</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>143.8±18.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83.4±9.4</td>
</tr>
<tr>
<td>Basal pulse rate (per min)</td>
<td>83.0±14.3</td>
</tr>
<tr>
<td>Glucose concentration (mg %)</td>
<td>101.6±25.8</td>
</tr>
<tr>
<td>Cholesterol concentration (mg %)</td>
<td>173.5±37.3</td>
</tr>
<tr>
<td>Left atrial diameter (cm)*</td>
<td>4.4±0.7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>40 (44)</td>
</tr>
<tr>
<td>Left atrial diameter &gt;3.5 cm*</td>
<td>39 (80)</td>
</tr>
<tr>
<td>Cardiomegaly (radiologist reading)</td>
<td>70 (77)</td>
</tr>
<tr>
<td>Complete left bundle branch block</td>
<td>5 (6)</td>
</tr>
<tr>
<td>New-onset fibrillation</td>
<td>61 (67)</td>
</tr>
<tr>
<td>Drug treatment</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>83 (91)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>73 (80)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>11 (12)</td>
</tr>
</tbody>
</table>

* n=49.

ables. Because there is clinical interest in a possible threshold at which these two variables have the most effect, we undertook a supplementary exploration of each. The patients were split into two groups with systolic blood pressures of ≤140 or >140 mm Hg as a categorical variable, and systolic blood pressure was retested for its association with a future event. This process was repeated at 5-mm Hg increments of blood pressure until the effect reached conventional significance (p<0.05). A similar process was repeated for age, beginning at age 60 years and using 5-year increments. The level at which systolic blood pressure became significant was 160 mm Hg and age, 75 years. There was no univariate association with future event for any other factor such as sex, diastolic blood pressure, basal pulse rate, increasing left atrial diameter, large heart size on chest x-ray film, complete left bundle branch block, blood glucose concentration, serum cholesterol concentration, hypertension, coronary artery disease, cardiomyopathy, congestive heart failure, alcoholism, other ICD-9-CM major diagnostic categories, or the use of aspirin, digoxin, diuretic or beta blocker.

Using the risk sets constructed for analyzing recurrent events, we estimated the effect of previous events on the risk of a subsequent event only. The hazard ratio for the number of previous events was 2.26 (95% CI 1.53–3.35). The second column of Table 2 shows the effect of individual factors after allowing for this effect of number of previous events. Factors that remained associated with subsequent events after adjusting for previous ones included systolic blood pressure of >160 mm Hg, age in years, and age of >75 years. When number of previous events, systolic blood pressure of >160 mm Hg, and age of >75 years were tested simultaneously, only previous embolic events and systolic blood pressure of >160 mm Hg retained a significant association. If events were limited to stroke alone, the following factors were individually associated: previous stroke (hazard ratio 3.72, 95% CI

TABLE 2. Factors Associated With Stroke and Other Embolic Events in Patients With Nonrheumatic Atrial Fibrillation

<table>
<thead>
<tr>
<th>Factor</th>
<th>First event (n=28)</th>
<th>Subsequent events (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-mm Hg intervals</td>
<td>1.26</td>
<td>1.01–1.59</td>
</tr>
<tr>
<td>&gt;160 mm Hg</td>
<td>6.40</td>
<td>2.32–17.63</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year intervals</td>
<td>1.29</td>
<td>1.02–1.63</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>2.51</td>
<td>1.14–5.51</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-mm Hg intervals</td>
<td>1.02</td>
<td>0.68–1.52</td>
</tr>
<tr>
<td>Increasing left atrial size (mm)</td>
<td>0.85</td>
<td>0.40–1.80</td>
</tr>
<tr>
<td>Large heart size</td>
<td>0.88</td>
<td>0.55–1.43</td>
</tr>
<tr>
<td>Complete left bundle branch block</td>
<td>2.03</td>
<td>0.70–5.93</td>
</tr>
<tr>
<td>Patient taking aspirin</td>
<td>2.52</td>
<td>0.86–7.39</td>
</tr>
</tbody>
</table>

Relative risk of subsequent events is calculated after adjusting for effect of previous event. Hazard ratios are calculated by taking natural antilogarithm of β coefficient estimated from proportional hazards model and are statistical estimates of relative risk associated with presence or incremental increase of each factor. CI, confidence interval.
2.04–6.79), systolic blood pressure (hazard ratio 1.03, 95% CI 1.01–1.06), and systolic blood pressure of >160 mm Hg (hazard ratio 8.2, 95% CI 2.57–26.15). When a previous stroke and systolic blood pressure of >160 mm Hg were tested simultaneously, the effect of blood pressure remained significant (hazard ratio 6.25, 95% CI 1.91–20.49).

If only the 61 patients who had documented new-onset NRAF were studied, there was a significant association between a subsequent event and previous ones (hazard ratio 1.84, 95% CI 1.17–2.88), aspirin use (hazard ratio 4.25, 95% CI 1.34–13.46), and complete left bundle branch block (hazard ratio 4.68, 95% CI 1.05–20.76). If these three factors were considered simultaneously, only previous events retained a significant association.

A potential weakness of our study is the selected nature of the patient population. Many of our patients were being followed after an initial visit to the emergency room or admission to the hospital. This study group was purposely chosen to obtain an event rate high enough to allow estimation of the risk of recurrence. For purposes of our analysis, the most important potential bias would occur if patients with stroke and other emboli, particularly recurrent ones, were especially selected for follow-up in some way. If, on the contrary, stroke victims died before 1982–1986, they would not be available to be a part of this study. To minimize these two possibilities, we created a smaller data set that included only the time at risk and the outcome events from January 1, 1982, forward (the time at which complete records on the practices screened were available). This restricted data set contained 41 patients who experienced 19 outcome events after 1982; eight of the 19 were recurrent events. Factors associated with a first event were the same as for the entire group.

Analyzing this data for the effect of previous events showed that the risk of a subsequent event was 3.4 ($p<0.0001$), for systolic blood pressure of >160 mm Hg the risk of a subsequent event was 5.6 ($p=0.0002$), and for age of >75 years the risk of a subsequent event was 1.6 ($p=0.2$). After adjusting for the effect of previous events, the effect of systolic blood pressure remained significant (hazard ratio 3.5, $p<0.05$). These results are similar in direction and magnitude to the entire cohort’s experience and are consistent with real associations rather than ones created by selection.

**Discussion**

Factors associated with an increased risk of first stroke or other embolic events in patients with NRAF in our retrospective study were systolic blood pressure (particularly if >160 mm Hg) and age (particularly if >75 years). There was no apparent association with sex, diastolic blood pressure, left atrial diameter, cardiomegaly, congestive heart failure, or other cardiac disease. These important negative findings confirm those reported from other studies. When only strokes (all types) were considered, systolic blood pressure, particularly if >160 mm Hg, was associated with future strokes. When only patients with new-onset NRAF were included, the presence of complete left bundle branch block and aspirin use were associated with future events.

When we considered recurrent events, previous events increased the risk of at least one subsequent event, compared with patients who never had an event, by 2.4 times. After adjusting for this effect of previous events, systolic blood pressure of >160 mm Hg and age of >75 years increased the risk of a future event still further. Restricting the analysis to stroke alone showed significant risk associated with previous stroke and with systolic blood pressure. When only patients with new-onset NRAF were studied, previous events, complete left bundle branch block, and aspirin use increased the risk of future events. Because our numbers are small, the latter two may represent chance findings. Also, clinicians might have been particularly adept at identifying patients at high risk and prescribing aspirin for them. In any case, there is no evidence from our study or from a randomized trial that aspirin use protects against embolic events in NRAF.

High systolic blood pressure may also be associated with stroke and embolic events in patients with NRAF, as found by ours and other studies. However, it is difficult to understand why diastolic blood pressure is not also associated. Elevated systolic blood pressure is a well known cause of hemorrhagic stroke and, as with previous cohort studies, we counted all stroke events. Therefore, it may be that a substantial benefit in preventing stroke will result from lowering the systolic blood pressure in a patient with NRAF. Similarly, age is an established risk indicator for stroke of all types, and this association may have been powerful enough to be apparent in our study without being a cause of embolic stroke specifically. Age was a factor in two published studies but not in a third. In any case, for patients >75 years old with high systolic blood pressure, the prospect of anticoagulant therapy is not appealing.

If the relative risk of recurrent embolism from our study is applied to the relative risk of first stroke in patients with NRAF, which according to two previous studies, is approximately 6, then it could be argued that subjects with NRAF and a first stroke or embolism are at approximately 13.5 times the risk of the normal population for recurrent events. This relative risk should be compared with that of stroke in patients with atrial fibrillation and rheumatic mitral valve disease (17). Trials to determine the efficacy of anticoagulants in this latter condition have never been carried out. In view of the evidence from one randomized trial for patients with NRAF, persons with a history of an embolic event should be strongly considered for chronic anticoagulation therapy.
Note added in proof. Since this paper was accepted for publication, Aronow et al. have reported a related study: 110 elderly patients with chronic atrial fibrillation were followed for 3 years for occurrence of stroke. Multivariate logistic regression showed a strong association between stroke and hypertension. Significant other factors were left ventricular hypertrophy, left atrial enlargement, and previous myocardial infarction.

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References

Key Words: atrial fibrillation, cerebrovascular disorders, embolism, risk factors
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