SUMMARY  The role of Atrial Fibrillation (AF) as a precursor of stroke was examined in the Framingham cohort based on 30 years of follow-up during which time 501 strokes occurred. There were 59 persons who sustained stroke in association with AF excluding those with rheumatic heart disease. AF increased the risk of stroke five-fold and the excess risk was found to be independent of the frequently associated cardiac failure and coronary heart disease. The contribution of AF to stroke risk was also at least as powerful as that of the other cardiovascular precursors.

Stroke associated with AF was not only independent and substantial but also imminent. There was a distinct clustering of stroke events at the time of onset of the AF. Thirty day case-fatality rates were no different in those with strokes accompanied by AF than not at 17% versus 19% respectively. Recurrences in those with AF were only slightly more frequent, 25% versus 20%, a difference that was not statistically significant. Stroke recurrence in the first 6 months following initial stroke was more than twice as common (47% versus 20%) in the AF group.

CHRONIC AF unassociated with rheumatic heart disease (RHD) has been found to be related to an increased incidence of stroke. Prospective epidemiologic study at Framingham, MA discloses stroke incidence following chronic nonrheumatic AF is increased more than five-fold even after age, sex, and the frequently associated hypertension is taken into account.¹

Some have suggested that paroxysmal, intermittent and recent-onset AF is particularly hazardous with an excess of stroke occurring in this group.² From the standpoint of prevention, clarification of this point is essential. We have studied the development of stroke in relation to duration of AF in a general population sample followed prospectively since 1950, comprising 30 years of follow-up. The purpose of the present report is to examine the time course of this threat of stroke, the likelihood and temporal pattern of stroke recurrences and case-fatality rates.

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Methods

We evaluated the development of stroke in 5184 men and women, aged 30 to 62, and free of stroke at entry followed for 30 years. Sampling procedure, criteria, and methods of examination have been described elsewhere.³ Subjects were examined every two years. Follow-up was satisfactory with 81% taking all possible examinations and less than five percent of the original cohort lost to mortality follow-up.

On each of the 16 biennial examinations, the subject was routinely questioned by a physician concerning habits, medications, and illnesses during the preceding two years. Physical examination and laboratory studies were made, and details surrounding all interim illnesses were sought. For stroke, including transient ischemic attacks (TIAs), surveillance was maintained by daily monitoring of all admissions to the only general hospital in town. If stroke was suspected, the patient was seen in the hospital by the study neurologist. Neurologic symptoms or signs noted by the study physician at biennial examination were followed by a detailed evaluation in the neurology clinic. The circumstances surrounding all illnesses and the death of each study subject were also sought by scrutiny of all available medical information, including hospital and physician records and post-mortem data. Prospectively, all data were reviewed by a panel of physicians to determine if minimal criteria were met for the diagnosis of the diseases under study and to determine the underlying cause of death. A neurologist has participated in reviews of suspected stroke cases for the past 20 years.

During the past 15 years most subjects were admitted to hospital by their personal physicians when
### TABLE 1
**Incidence of Stroke by Type, 30 Year Follow-up**

<table>
<thead>
<tr>
<th>Stroke with AF (RHD excluded)</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>brain infarction</td>
<td>130</td>
<td>137</td>
<td>267</td>
</tr>
<tr>
<td>transient ischemic attack only</td>
<td>27</td>
<td>26</td>
<td>53</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>subarachnoid</td>
<td>17</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>intracerebral</td>
<td>14</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>RHD and stroke</td>
<td>3</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Cerebral embolus (other)</td>
<td>14</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>241</td>
<td>260</td>
<td>501</td>
</tr>
</tbody>
</table>

stroke or TIA was suspected. Most had lumbar puncture, brain scan, EEG and skull radiographs prior to CT scan availability. In recent years at least one CT scan has been done soon after admission on most subjects with stroke or TIA. Cerebral arteriography was done infrequently in patients with stroke in the presence of AF or other obvious source of emboli. General post-mortem examinations were made in 40% of decedents; the brain was examined in half of those autopsied.

In addition to noting the presence of AF on ECG during biennial exam, AF was sought during review of all interim hospitalizations. Duration of AF was measured from the time of first documentation by ECG available for review. AF was often documented for the first time at the time of admission for stroke. In those instances no judgement as to the short term duration of AF could be made. Anticoagulants were not in use to any significant extent in this group at time of onset or recurrence.

Since it is often not possible to distinguish thrombotic from embolic stroke all strokes occurring in persons with AF were counted without respect to probable stroke mechanisms. Analyses relating AF to stroke was restricted to persons with AF unassociated with RHD. CHF and CHD are frequent precursors of stroke with or without AF. To determine the additional role of AF as a risk factor for stroke, a multiple logistic regression was performed. The variables age, CHD, CHF, and systolic blood pressure were considered. The logistic coefficients were estimated using an iterative maximum likelihood approach.4

### Results

After 30 years of follow-up 501 cases of stroke occurred; 241 in men and 260 in women (table 1). Atherothrombotic Disease, Brain Infarction and TIAs Only, accounted for 64% of the total. Thirteen percent were due to Intracranial Hemorrhage; Subarachnoid Hemorrhage twice as often as Intracerebral Hemorrhage, and 3% were due to other uncommon causes. Strokes occurring in persons with RHD (3%) were excluded from this analysis. Excluding these 17 persons with RHD, and an additional 29 with an embolic source other than AF, left 59 persons who sustained a stroke in the presence of AF.

Since AF often occurs in persons with stroke-inducing impaired cardiac function, notably congestive heart failure and coronary heart disease and is directly related to age and systolic blood pressure, a multivariate logistic analysis including these variables and AF was done (table 2). Each of the variables are significantly related to stroke incidence and each makes a contribution that is independent of the other factors. Not only does AF make a contribution to stroke risk that is independent of coronary heart failure and coronary heart disease, the size of the coefficient, (beta), for AF is also greater than for either of these variables showing AF to be at least as powerful as these three co-factors.

When distribution of cases of stroke is examined in relation to duration of AF prior to stroke a clustering close to onset of AF is seen (fig. 1). Nearly a quarter, 14 of 59, had AF noted for the first time during hospitalization for stroke. An additional eight cases (14%) occurred in the first twelve months following the onset of AF. Thereafter, stroke occurred at about 5% per year.

### TABLE 2
**Multivariate Logistic Coefficients for Relating Specified Variables to the Incidence of Stroke in Two Years. The Framingham Heart Study, 26 Year Follow-up. Men and Women 45 Years and Older Free of Stroke at Risk.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.0082</td>
<td>10.36*</td>
</tr>
<tr>
<td>SBP</td>
<td>.0187</td>
<td>10.89*</td>
</tr>
<tr>
<td>CHF</td>
<td>.7607</td>
<td>3.61*</td>
</tr>
<tr>
<td>CHD</td>
<td>.6789</td>
<td>5.27*</td>
</tr>
<tr>
<td>Atrial fibrillation†</td>
<td>1.0082</td>
<td>4.52*</td>
</tr>
</tbody>
</table>

*p < 0.01.
†RHD excluded.
AF are available, rational therapy may be outlined and clinical trials conducted. In a study of chronic AF in this population it was found that those with RHD had a 17-fold increased risk of stroke. Persons with nonrheumatic chronic AF documented at biennial examination, had more than a five-fold increased risk of stroke even after age and the often associated hypertension were taken into account. Recent interest in the epidemiologic features of AF, particularly in its precursors, combined with therapeutic enthusiasm in stroke prevention has focused attention on this cardiac arrhythmia.9, 10 In elderly populations, AF has been present and presumably related to 10% to 20% of all stroke events.11-14 In the present report, 12% of initial strokes in this general population sample occurred in the presence of AF without valvular heart disease. Since AF incidence rises with age its contribution to stroke occurrence can be expected to rise in the United States, as it will in this cohort as it ages.

Onset of AF is clearly temporally related to immi- nence of stroke. AF is present at the time of stroke onset in 24% and within six months of onset in about a third of AF associated strokes. Patients with recent onset of AF are certainly at high risk and warrant vigorous preventive measures. AF commonly follows the development of overt cardiovascular disease particularly congestive heart failure and hypertensive cardiovascu lar disease and prevention of these conditions may be the best prophylaxis for AF. Even in the presence of hypertension, congestive failure, and coronary heart disease, AF makes a significant independent contribution to stroke incidence. Recurrence, like initial onset, seems to cluster in the early months again encouraging prompt and vigorous efforts be made if stroke is to be prevented.

In a surgical series of patients recuperating from peripheral arterial embolectomy, recurrence was common, 50% sustained at least one recurrence, and occurred soon after the initial embolism.15 Among those patients with nonrheumatic AF as the source, recurrence occurred within four days in 26%, within two weeks in 47%, and within four months in 68%.

There is reason to believe the bulk of strokes occurring in persons with AF are on the basis of cerebral embolism, although AF does reduce cerebral blood flow and could thereby contribute to stroke.13-16 Efforts at stroke prevention in patients with nonvalvular AF undoubtedly will rest in therapies that interfere with intra-atrial thrombus formation. A controlled trial of antithrombotic agents or anticoagulants for stroke prevention in nonrheumatic AF and particularly in recent onset AF seems long overdue.

**References**


Duration of atrial fibrillation and imminence of stroke: the Framingham study.
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