Time Trends of Ischemic Stroke Incidence and Mortality in Patients Diagnosed With First Atrial Fibrillation in 1980 to 2000

Report of a Community-Based Study

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Background and Purpose—With the changes in management of atrial fibrillation (AF) over time, it is possible that the time trends of post-AF stroke incidence and mortality have changed. We sought to determine whether the incidence and survival of ischemic stroke after AF diagnosis have improved.

Methods—We identified the Olmsted County, Minn, residents who developed first AF from 1980 to 2000 and followed them in medical records to 2004. The outcomes were first ischemic stroke and death.

Results—Of the 4117 subjects diagnosed with first AF and without previous stroke, 446 (11%) sustained a first ischemic stroke during a mean follow-up time of 5.5±5.0 years. The age- and sex-adjusted incidence of stroke decreased, on average, by 3.4% per year (P<0.0001), concurrent with an increase in warfarin and aspirin use (both P<0.0001) and reduction of systolic blood pressure (P<0.001). The age-adjusted ischemic stroke incidence was higher in women (P=0.039), but not after adjusting for systolic blood pressure (P=0.41). Compared with the general Minnesota white population, the relative mortality hazard ratio was 1.88 for men and 1.84 for women without stroke and 3.03 for men and 3.80 for women (P<0.05) with stroke. The relative mortality hazard did not vary by age or calendar year of AF diagnosis.

Conclusions—Post-AF ischemic stroke incidence decreased significantly from 1980 to 2000, during which time a substantial increase in the use of antithrombotic therapy and reduction of systolic blood pressure was evident. The relative mortality risk of stroke, however, had not improved over time. (Stroke. 2005;36:2362-2366.)

Key Words: atrial fibrillation • incidence • stroke
difference in the time trends of incidence and mortality of stroke. Ascertainment of stroke was accomplished through review of the medical records. Ischemic stroke was defined as the acute onset of a focal neurological deficit persisting for >24 hours, compatible with altered circulation to a limited region of the cerebral hemispheres, brain stem, or cerebellum, with or without evidence on computed tomography or MRI. Nonhemorrhagic infarctions from hematologic cause, vasculitis, or hemostatic factors were excluded. The method of ascertainment of stroke, as well as other outcomes, and definitions for all of the conditions were the same for the entire 21-year period.

Definition of Covariates
Chronic versus paroxysmal AF was defined by whether there were recognizable intervening episodes of sinus rhythm. Silent AF was asymptomatic and discovered incidentally. Coronary artery disease was defined by angiographic findings of lesions ≥50% in any of the 3 main arterial distributions, angina, or history of myocardial infarction. Myocardial infarction was defined by at least 2 of the 3 diagnostic criteria: compatible clinical presentation, diagnostic cardiac enzyme levels, and consistent electrocardiographic changes. Clinically diagnosed valvular heart disease was defined by presence of a murmur on physical examination, with or without echocardiographic confirmation. Echocardiographically confirmed valvular heart disease was defined by greater than mild stenosis or regurgitation, or prior valve repair/replacement. Congestive heart failure was defined by the presence of 2 major or 1 major and 2 minor Framingham criteria.

Coronary artery disease was defined by the presence of ≥50% stenosis based on neurovascular imaging or previous intervention. Transient ischemic attack referred to ischemic cerebral dysfunction lasting <24 hours with neither sequelae nor any lesion on imaging. Systemic hypertension was defined by a physician’s diagnosis with medical therapy for elevated blood pressure, documented systolic blood pressure of ≥140 mm Hg, or diastolic blood pressure of ≥90 mm Hg on ≥2 separate measurements, excluding those in the context of an acute illness or injury. Dyslipidemia was defined by a total cholesterol ≥200 mg/dL, triglycerides ≥150 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, high-density lipoprotein cholesterol <40 mg/dL on ≥2 occasions, or treatment with lipid-lowering agents. Diabetes mellitus was defined by physician’s diagnosis and treatment with insulin or oral hypoglycemic agents. Cardiomyopathy and chronic renal disease were based on documented clinical diagnosis.

Statistical Analyses
Baseline characteristics were summarized by mean and SD or frequency percents and assessed for trends across the calendar year of AF diagnosis, considered as a continuous variable, by linear regression analysis for continuous variables and logistic regression analysis for binary variables, with adjustment for age and sex. The overall and sex-specific cumulative incidence of first stroke after AF was estimated using the Kaplan-Meier method. The trend of stroke incidence was assessed using the Cox proportional hazards model with age, sex, and calendar year of AF diagnosis in the model, as well as stratifying on sex and including age and calendar year of AF diagnosis. We assessed for both a linear time trend and for a reduction in incidence in the last period: 1995 to 2000. Cox models for prediction of time to stroke based on clinical variables at time of first AF event were developed. The association of first stroke with AF diagnosis was estimated using time-dependent proportional hazards models with age, sex, and calendar year of AF diagnosis as covariates, in addition to the time-dependent variable of stroke. Trends, as well as sex and age effects, and interactions of year with age and sex in the use of warfarin and aspirin were assessed using logistic regression. Relative to the general Minnesota white population, mortality ratios were calculated by dividing the observed number of mortality events by an “expected number” of deaths, defined as the sum of the cumulative hazards, applying the fact that the negative logarithm of the standard Minnesota white life-table survival probability up to each individual’s follow-up time can be treated as a (right-censored) negative exponential survival time with mean 1. The sum of these exponential survival times (overall or subgroups from the intervals before and after stroke) can be treated as the expected numbers of events for these same individuals, under the null hypothesis that survival follows the reference life-table distribution.

Results
A total of 4618 subjects were confirmed to have first AF during 1980–2000, mean age 73±14 years (range 18 to 107 years), and 2365 subjects (51%) were men. Of these, 403 subjects had previous ischemic stroke, and 98 sustained the first ischemic stroke and AF on the same day. Of the remaining 4117 subjects (mean age 72±15 years; 51% men), 446 (11%; mean age 77±11 years; 38% men) had a first ischemic stroke during a mean follow-up of 5.5±5.0 years, and 2713 subjects (66%) died. Their baseline characteristics are displayed in Table 1.

Incidence of Ischemic Stroke After AF Diagnosis
The cumulative incidence of first ischemic stroke increased with time (10% at 5 years and 17% at 10 years; Figure 1), higher in women than in men (21% versus 14% at 10 years; P<0.0001). Female sex was predictive of first ischemic stroke after age adjustment (hazard ratio [HR], 1.23; 95% CI, 1.01 to 1.51; P=0.039) but was not significant once adjusted for systolic blood pressure (P=0.41). Systolic blood pressure was the only variable that, when adjusted with age, could eliminate the sex difference in stroke risk. The proportion of women with systolic blood pressure >140 mm Hg was significantly higher (997 women, 50%; 705 men, 33%; P<0.0001).

In a multivariate model, age (HR, 1.05; 95% CI, 1.04 to 1.06; P<0.0001), systolic blood pressure >140 mm Hg (HR, 1.71; 95% CI, 1.38 to 2.12; P<0.0001), systemic hypertension (HR, 1.61; 95% CI, 1.13 to 2.30; P=0.009), coronary artery disease (HR, 1.27; 95% CI, 1.04 to 1.54; P=0.018), diabetes mellitus (HR, 2.09; 95% CI, 1.67 to 2.62; P<0.0001), and the absence of warfarin use before stroke (HR, 2.27; 95% CI, 1.71 to 3.03; P<0.0001) were independently predictive of ischemic stroke, whereas calendar year of AF diagnosis was negatively associated with stroke (HR, 0.97; 95% CI, 0.95 to 0.99; P<0.001).

Trends of Ischemic Stroke, Antithrombotic Use, and Blood Pressure
There was a significant reduction in the incidence of stroke after first AF for the study population (n=4117) over time. This trend in significant stroke reduction was not different, even if the patients who had first AF and stroke diagnosed on the same day (n=98) were included in the analysis. The age- and sex-adjusted stroke incidence decreased, on average, by 3.4% per year (P=0.0001) over the study period, and the time trends are depicted in Figure 2. The decrease in ischemic stroke was significant for both men (5% per year; P<0.001) and women (2.5% per year; P=0.023), but the rate of decline did not differ between the sexes (P=0.22). The reduction of stroke as a linear trend was not significant (P=0.56) when tested simultaneously for a reduction from 1995 to 2000 (HR, 0.59; 95% CI, 0.42 to 0.83; P=0.003) using the Cox model. The significant reduction of stroke occurred primarily from 1995 to 2000 (Figure 2).
The use of warfarin and aspirin increased significantly over time (Table 2) and was comparable between the sexes (warfarin $P=0.19$; aspirin $P=0.20$). We calculated the stroke risk at year 5 after AF diagnosis, unadjusted and adjusted for warfarin, assuming a stroke risk reduction of 68% with warfarin use for 1 year based on published literature (relative risk of 0.32). The Kaplan-Meier stroke risks were 11.1% (unadjusted) and 12.1% (adjusted) for 1980–1984 and 6.6% (unadjusted) and 11.7% (adjusted) for 1995–2000. Warfarin use contributed much to the decline in stroke risk.

Systolic blood pressure also improved over time (Table 1). The reduction of age- and sex-adjusted stroke incidence was, on average, 3.4% per year when unadjusted for systolic blood pressure.
pressure and 2.9% per year, on average, when adjusted for systolic blood pressure.

**Impact of Stroke on Survival and Time Trends**

Before stroke, AF was associated with an increase of relative mortality risk by 85% above that of age-expect for both men and women. Women had lower relative mortality than men after AF diagnosis, in exact proportion to their advantage in the general population (men relative mortality HR, 1.88; 95% CI, 1.77 to 1.99; women relative mortality HR, 1.84; 95% CI, 1.73 to 1.95). However, after stroke, the age-adjusted survival became similar for the sexes. The relative mortality hazard was greater in women (men 3.03, 95% CI, 2.49 to 3.57; women 3.80, 95% CI, 3.31 to 4.30; \( P < 0.05 \)) but did not vary with age or calendar year of AF diagnosis. The number of observed and expected deaths for the entire period and before and after stroke are shown in Table 3. There was no detectable improvement in the survival of AF patients who had sustained a stroke over time.

**Discussion**

Our study provided evidence of the following: (1) there was a significant decrease in post-AF ischemic stroke incidence from 1980 to 2000; (2) there was a substantial increase in the use of antithrombotic therapy and reduction of systolic blood pressure; (3) there were no gender differences of post-AF stroke incidence once adjusted for age and systolic blood pressure; and (4), the relative mortality risk after stroke had not changed over time.

**Stroke Risk After First AF and Time Trends**

We have confirmed that women had higher risk of stroke after AF as shown in other studies.\(^1\)\(^5\),\(^1\)\(^6\) Additionally, we provided new data regarding the trends of stroke risk over time. The reduction of stroke incidence, most significantly in the period 1995 to 2000, probably reflects the modification of clinical practice with the use of warfarin for prophylaxis against thromboembolic events, which has been shown to be efficacious.\(^6\)\(^–\)\(^1\)\(^1\)

**TABLE 3.** **Sex-Specific Mortality Ratios Relative to the General Minnesota White Population After AF Diagnosis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
</tr>
<tr>
<td>Overall</td>
<td>1247</td>
<td>637.82</td>
</tr>
<tr>
<td>Prestroke</td>
<td>1120</td>
<td>595.93</td>
</tr>
<tr>
<td>Poststroke</td>
<td>127</td>
<td>41.89</td>
</tr>
</tbody>
</table>

Patients who had an ischemic stroke within 14 days after AF diagnosis were excluded (n=32).

The proportion of patients with systolic blood pressure >140 mm Hg over time, which likely had contributed to the reduction of stroke risk.

Although studies have demonstrated the underutilization of warfarin, especially in women, for stroke prevention in AF,\(^1\)\(^7\)\(^–\)\(^2\)\(^5\) female sex was not independently related to warfarin or aspirin use in our study. Some studies have shown that the efficacy of warfarin is lower in women,\(^2\)\(^6\) but this could not be analyzed in our study. There have also been data suggesting that women are more frequently undertreated for hypertension.\(^2\)\(^7\) Indeed, the proportion of female patients with systolic blood pressure >140 mm Hg was significantly higher than in men. Poorer blood pressure control in women could have contributed to the higher age-adjusted stroke risk in women with AF in this study.

**Time Trends of Mortality Risk Associated With Post-AF Stroke**

Strokes associated with AF are generally large, more disabling,\(^2\)\(^8\),\(^2\)\(^9\) and more likely to be fatal.\(^2\)\(^8\)–\(^3\)\(^0\) The high-relative mortality risks associated with stroke after AF for both sexes, as well as the greater age-adjusted relative mortality risk in women when compared with men, did not change over time. The underlying mechanisms for the gender differences could not be elucidated in this study, although atrial remodeling, thrombotic tendencies,\(^3\)\(^1\) and difference in the efficacy of warfarin\(^2\)\(^6\) have all been proposed as possibilities.

**Limitations**

There are inherent biases associated with the retrospective design. The identification of AF cases relied on confirmation by ECG and that the patients were seen at the Mayo Clinic. Patients might not have been included because their AF was silent and undetected. Thus, the incidence of AF or stroke could have been underestimated. The stroke incidence could also have been affected by the changing distribution of AF etiologies over time, but etiologic classification could not be precise, especially with respect to valvular or nonvalvular reasons, because echocardiography was not consistently used. The population of the Olmsted County, Minn, is predominantly white, and the extent to which we can generalize the findings to other ethnic/racial groups remains to be determined.

**Conclusions**

The incidence of ischemic stroke in AF patients has decreased over the past 2 decades. The marked increase in the use of antithrombotic therapy and the improved control of blood pressure appeared to have played important roles.
Despite the improvement in stroke incidence, the relative mortality risk of stroke after AF and gender differences have not changed.

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References
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