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# Contribution of Atrial Fibrillation to Incidence and Outcome of Ischemic Stroke

## Results From a Population-Based Study

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***Background and Purpose***—Atrial fibrillation (AF) is a major risk factor for ischemic stroke and its prevalence increases steeply with age. Population-based data on its influence on stroke outcome are scarce.

***Methods***—We evaluated the prevalence of AF and its influence on prognosis in patients with a first-ever ischemic stroke from a population-based registry.

***Results***—The presence of AF at stroke onset and during the acute phase was confirmed by a standard electrocardiogram in 869 (24.6%) of 3530 patients with ischemic stroke. With respect to patients without the arrhythmia, those with AF were more frequently women, aged 80 years and older, with coronary heart disease and peripheral arterial disease. The presence of AF was associated with high 30-day (32.5%; 95% CI, 29.3 to 35.6) and 1-year case-fatality rates (49.5%; 95% CI, 46.2 to 52.8), with a higher stroke recurrence rate within the first year of follow-up (6.6% versus 4.4%; $P=0.046$) and with the worst survival after an average follow-up of 45.2 months ($P<0.0001$). At the multivariate Cox regression analysis, AF was an independent predictor of 30-day and 1-year mortality. Approximately 17% of all deaths were attributable to the presence of AF.

***Conclusions***—We found a high prevalence of AF in patients with a first-ever ischemic stroke, especially among elderly women. The overall contribution of AF to stroke mortality was relevant, suggesting that together with new strategies to prevent the development of the arrhythmia more appropriate treatments are needed, mostly in elderly women. **(*Stroke*. 2005;36:1115-1119.)**

**Key Words:** atrial fibrillation ■ mortality ■ outcome ■ stroke, ischemic

Atrial fibrillation (AF) is a common arrhythmia and a major risk factor for ischemic stroke, especially in the elderly.[1–4] Its prevalence is <1% in the general population, ≈6% in people older than 65 years of age, and increases up to 9% at the age of 80 to 89 years.[1,2,4,5] Patients with nonvalvular AF have a 5-fold excess risk of stroke.[4–7] However, population-based data are scarce in patients who have experienced a first-ever ischemic stroke in the presence of AF regarding long-term risk of stroke recurrence and case-fatality rate.[2–4,6,8] We evaluated the prevalence of AF and its influence on prognosis in patients with a first-ever ischemic stroke.

## Subjects and Methods

The prevalence of AF and its influence on prognosis were evaluated in patients with a first-ever ischemic stroke included in a 5-year period (1994–1998) in the prospective, population-based L'Aquila registry, which complies with epidemiological criteria for stroke incidence studies.[9] The study was approved by the institutional ethics committee and complies with national rules on informed consent of subjects involved in the study. Stroke was defined as rapidly developing signs of focal or global disturbance of cerebral function, lasting >24 hours, or leading to death, with no apparent cause other than that of vascular origin.[10] For the purpose of the present study only patients with cerebral infarction (codes 433 and 434, *International Classification of Diseases*, 9th Revision [ICD-9]) were considered.[11] A probable ischemic stroke was diagnosed in the absence of brain neuroimaging or necropsy examinations and of clinical symptoms reflecting increased intracranial pressure such as headache and vomiting, decreased alertness or coma, and gradual progression to death within 24 hours of onset. Ischemic stroke type was categorized according to the criteria of the Oxfordshire community stroke project (OCSP).[12] The study population was identified by residency lists and included 297 838 individuals at the 1991 census.[13] To be included in the study, patients who had a first-ever stroke had to reside in the L'Aquila district at the time of the stroke occurrence. All events occurring in the study population were identified by active monitoring of all inpatient and outpatient health services. All patients had to be seen by a consulting neurologist to validate the event. Nearby hospitals were also regularly monitored to identify those residents who had cross-boundary medical care. The study purpose was explained in advance to all general practitioners and on-call physicians who were asked to refer all stroke cases and give information about patients evaluated at home. Death certificates were checked monthly and clinical details of all deceased patients

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with a diagnosis of stroke were reviewed. Completeness of case ascertainment was assessed by means of a capture–recapture technique. Study population and methodology were detailed in a previous paper referring to 819 patients identified and included in the registry during the first of the 5-year inclusion period.[13] The presence of AF at stroke onset and during the acute phase had to be confirmed by a standard 12-lead electrocardiogram (ECG) showing replacement of consistent P waves by rapid oscillations of fibrillatory waves that varied in size, shape, and timing, associated with an irregular ventricular response.[2,14] Regular RR intervals were possible in the presence of AV block or interference by ventricular or junctional tachycardia. Patients without ECG evaluation on admission were excluded from the analyses. Paroxysmal atrial fibrillation was diagnosed in patients with spontaneous conversion to sinus rhythm;[1,4,14,15] chronic or permanent atrial fibrillation was defined as the persistence of the rhythm disturbance assessed by ECG and medical history.[2,4] First detected episodes of AF were included in the paroxysmal group, when self-limited, or in the permanent group if sustained, whereas persistent AF was included in the chronic or permanent group.[2,4] Valvular atrial fibrillation was assessed in the presence of a prosthetic heart valve or of rheumatic mitral stenosis confirmed by transthoracic echocardiography;[2,4,14] lone atrial fibrillation was diagnosed in patients younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease;[2,4] AF of otherwise uncertain origin was defined as *idiopathic*.[4] All cases were followed-up by quarterly planned visits or by telephone interview, either in person or with a close relative or with the general practitioner, up to December 31, 2001. Outcome events to be considered during the follow-up were nonfatal stroke recurrence and death from cardiovascular or non cardiovascular causes.[13]

Etiologic fraction for AF was calculated as the population attributable risk, based on the 5-fold relative risk reported in the literature[4–7] and the prevalence rate of AF that we found in our series of first-ever ischemic stroke. Pearson $\chi^2$ test or Student $t$ test were used to compare groups as appropriate. Odds ratios with 95% confidence intervals were used as a measure of the association between AF and vascular risk factors. A logistic multiple regression model was used to identify risk factors independently associated with AF. Survival curves were estimated by the Kaplan–Meier method. Comparisons between survival curves for patients with and without AF were performed by the log-rank test. Multivariate estimates of the hazard ratios were calculated according to the Cox regression analysis. Two-sided probability values $<0.05$ were considered to indicate statistical significance. All analyses were performed with the SPSS statistical software (SPSS).[16]

## Results

During the study period, we identified 3594 patients with a first-ever ischemic stroke. After the exclusion of 64 patients (1.8%) without ECG evaluation on admission, AF was documented in 869 (24.6%) of 3530 patients. Three hundred forty (39.1%) were men and 529 (60.9%) were women; mean age at stroke onset was 78.8±13.3 years (77.1 years in men and 79.9 years in women; $P=0.002$).

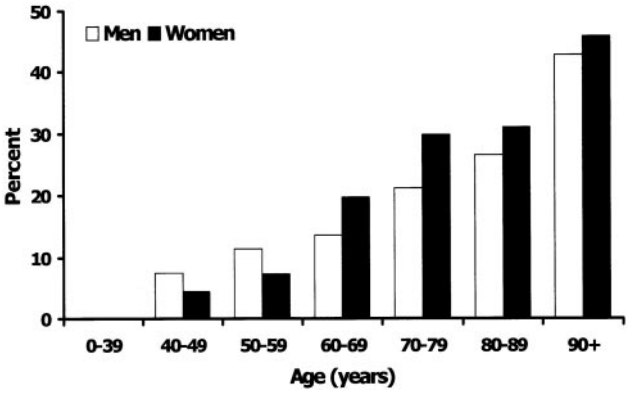


**Figure 1.** Prevalence of atrial fibrillation according to age and sex.

As shown in Figure 1, the prevalence of AF increased with age in both sexes, from 4.4% in patients younger than 50 years up to 44.7% in those 90 years and older, and was higher in women than in men after the age of 60 years. By assuming the reported relative risk of 5 for AF, the estimated etiologic fraction was 19.7% for the whole cohort. Eight hundred thirty-six patients (96.2%) were hospitalized. Seven hundred sixty-eight patients (88.4%) underwent brain CT (n=685), MRI (n=73), or both (n=10) at least once; the remaining 101 (11.6%) patients had a probable ischemic stroke diagnosed according to clinical criteria. AF was chronic in 814 patients (93.7%) and paroxysmal in 55 (6.3%). Chronic AF was nonvalvular in 674 (82.8%) patients, valvular in 57 (7.0%), and lone or idiopathic in 83 (10.2%).

With respect to patients without the arrhythmia, those with AF (Table 1) were mostly women, aged 80 years and older, with coronary heart disease, and peripheral arterial disease, and were less frequently hypercholesterolemic and cigarette smokers. The multivariate logistic regression analysis including all variables in the model confirmed all the associations but that with cigarette smoking. Moreover, there were more total anterior (38.3% versus 25.5%) and less posterior circu-

**TABLE 1. Baseline Characteristics of First-Ever Ischemic Stroke Patients With and Without Atrial Fibrillation**

| Characteristics | AF−, (N=2661), No. (%) | AF+, (N=869), No. (%) | OR, 95% CI | *P* |
|---|---|---|---|---|
| Female/male | 1325/1336 | 529/340 | 1.57 (1.34–1.83) | <0.0001 |
| Age ≥80 y | 875 (32.9) | 398 (45.8) | 1.75 (1.50–2.04) | <0.0001 |
| Arterial hypertension | 1734 (65.2) | 535 (61.6) | 0.86 (0.73–1.00) | 0.0547 |
| Diabetes mellitus | 700 (26.3) | 210 (24.2) | 0.91 (0.76–1.08) | 0.2800 |
| Coronary heart disease | 632 (23.8) | 297 (34.2) | 1.67 (1.41–1.97) | <0.0001 |
| Hypercholesterolemia | 768 (28.9) | 167 (19.2) | 0.59 (0.49–0.71) | <0.0001 |
| Cigarette smoking | 698 (26.2) | 164 (18.9) | 0.65 (0.54–0.79) | <0.0001 |
| Peripheral arterial disease | 290 (10.9) | 146 (16.8) | 1.65 (1.33–2.05) | <0.0001 |

AF indicates atrial fibrillation; CI, confidence interval; OR, odds ratio.

**TABLE 2. 30-Day and 1-Year Case-Fatality Rates by Atrial Fibrillation Type**

| | 30-Day | | | 1-Year | | |
|---|---|---|---|---|---|---|
| Atrial fibrillation | No. | CFR | 95% CI | No. | CFR | 95% CI |
| All without (n=2661) | 432 | 16.2% | 14.8–17.6 | 720 | 27.1% | 25.4–28.7 |
| All with (n=869) | 282 | 32.5% | 29.3–35.6 | 430 | 49.5% | 46.2–52.8 |
| Paroxysmal (n=55) | 15 | 27.3% | 15.5–39.0 | 24 | 43.6% | 30.5–56.7 |
| Chronic (n=814) | 267 | 32.8% | 29.6–36.0 | 406 | 49.9% | 46.4–53.3 |
| Nonvalvular (n=674) | 234 | 34.7% | 31.1–38.3 | 353 | 52.4% | 48.6–56.1 |
| Valvular (n=57) | 10 | 17.5% | 7.7–27.4 | 16 | 28.1% | 16.4–39.7 |
| Lone/idiopathic (n=83) | 23 | 27.7% | 18.1–37.3 | 37 | 43.6% | 30.5–56.7 |

CFR indicates case-fatality rate.

lation (7.8% versus 11.6%) and lacunar infarcts (9.6% versus 18.5%) in patients with AF than in those without AF, whereas partial anterior circulation infarcts occurred in similar proportions in both groups ($P<0.0001$; $\chi^2$ test).

After the index event, most of the patients were prescribed antiplatelet agents (74.2%), whereas only 11.3% were prescribed oral anticoagulants. The proportion of patients on antiplatelet treatment ranged from 73.1% in those with partial anterior circulation infarcts to 77.9% in those with posterior circulation infarcts ($P=0.74$), whereas the corresponding proportion of patients on oral anticoagulants ranged from 8.8% in patients with posterior circulation infarcts to 12.3% in those with total anterior circulation infarcts ($P=0.85$). Mean duration of follow-up was 45.2 months (maximum 96 months). As shown in Table 2, in patients with AF the 30-day case-fatality rate was 32.5% (95% CI, 29.3 to 35.6) and the 1-year case-fatality rate was 49.5% (95% CI, 46.2 to 52.8). Patients with valvular AF, mostly as a consequence of their younger age (72.1 versus 79.7 years; $P=0.0001$), had better 30-day (17.5% versus 34.7%; $P=0.014$) and 1-year (28.1% versus 52.4%; $P=0.0008$) case-fatality rates with respect to patients with nonvalvular AF.

The rate of nonfatal and fatal stroke recurrence within the first year of follow-up (Figure 2) was slightly higher in patients with AF than in those without the arrhythmia (6.9% versus 4.7%; $P=0.0398$), whereas the long-term survival (Figure I, available online only at http://www.strokeaha.org) was worse in patients with AF (25.4% versus 49.7; $P<0.0001$; log-rank test). Annual mortality rates (Table 3) were higher in patients with AF than in those without the arrhythmia at 1 year (49.5% versus 27.1%) and decreased proportionally thereafter in both groups.

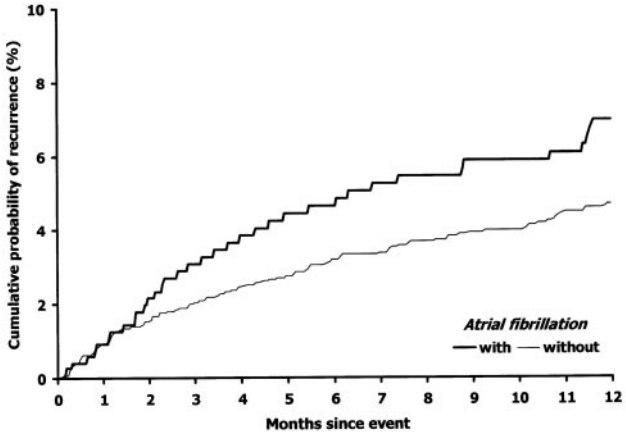


**Figure 2.** Kaplan–Meier estimates of the likelihood of recurrent stroke in patients with and without atrial fibrillation ($P=0.0398$).

At the multivariate Cox regression analysis including age, sex, impaired consciousness, stroke type, and vascular risk factors as covariates, AF was an independent predictor of 30-day and 1-year mortality (Table 4), but not of 1-year stroke recurrence. The computation of the attributable death risk at 1 year, using the case-fatality rates obtained in patients with and without the arrhythmia (49.5% versus 27.1%) and the prevalence rate of AF that we found (24.6%), indicated that ≈17% of the stroke patients died because of the presence of AF.

## Discussion

The role of AF was investigated in a large population-based cohort of patients who had a first-ever ischemic stroke documented with brain neuroimaging and cardiological examinations. Completeness of case ascertainment allowed precise estimation of the prevalence of the arrhythmia and of the prognosis after the index event. The high rate of hospital admissions (96.2%) might have contributed to identify AF in older patients.

The 24.6% prevalence rate of AF among our patients was higher than in other population-based studies (9.3% to 19.0%) and clinical series (16.7% to 18%) and mostly depended on the high mean age of the patients at stroke onset (78.8±13.3 years)

**TABLE 3. Annual Mortality Rates in Patients With and Without Atrial Fibrillation**

| | AF− | | AF+ | |
|---|---|---|---|---|
| Year | Rate, % | 95% CI | Rate, % | 95% CI |
| 1 | 27.1 | 25.3–28.8 | 49.5 | 46.1–52.8 |
| 2 | 8.2 | 7.1–9.4 | 14.1 | 10.8–17.5 |
| 3 | 6.1 | 4.9–7.3 | 13.5 | 10.0–17.1 |
| 4 | 6.0 | 4.8–7.2 | 10.1 | 6.8–13.5 |
| 5 | 5.5 | 4.3–6.6 | 11.3 | 7.7–14.8 |
| 6 | 3.4 | 2.4–4.4 | 3.6 | 1.3–6.0 |
| 7 | 3.7 | 2.5–4.9 | 5.4 | 2.1–8.7 |
| 8 | 2.5 | 1.3–3.6 | 3.8 | 0.3–7.4 |

**TABLE 4. Predictors of 30-Day and 1-Year Mortality in Patients With a First-Ever Ischemic Stroke**

| | 30-Day | | 1-Year | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Atrial fibrillation | 1.47 (1.25–1.72) | <0.0001 | 1.51 (1.30–1.74) | <0.0001 |
| Male | 1.18 (0.99–1.40) | 0.0555 | 1.17 (1.00–1.36) | 0.0501 |
| Age* | 1.59 (1.44–1.74) | <0.0001 | 1.80 (1.65–1.96) | <0.0001 |
| Arterial hypertension | 1.01 (0.86–1.18) | 0.9215 | 0.89 (0.77–1.02) | 0.0967 |
| Diabetes mellitus | 1.52 (1.30–1.79) | <0.0001 | 1.48 (1.29–1.72) | <0.0001 |
| Coronary heart disease | 1.07 (0.91–1.26) | 0.4131 | 1.15 (0.99–1.33) | 0.0654 |
| Hypercholesterolemia | 0.88 (0.73–1.06) | 0.1660 | 0.88 (0.75–1.04) | 0.1379 |
| Cigarette smoking | 0.68 (0.54–0.85) | 0.0008 | 0.78 (0.63–0.95) | 0.0149 |
| Peripheral arterial disease | 0.78 (0.62–0.98) | 0.0313 | 0.95 (0.78–1.15) | 0.5962 |
| Impaired consciousness | 4.23 (3.54–5.06) | <0.0001 | 3.52 (2.99–4.13) | <0.0001 |
| Stroke type | | | | |
| PACI | 1.00 | | 1.00 | |
| TACI | 1.82 (1.50–2.20) | <0.0001 | 1.78 (1.50–2.10) | <0.0001 |
| POCI | 0.77 (0.55–1.07) | 0.1201 | 0.68 (0.51–0.92) | 0.0129 |
| LACI | 0.45 (0.30–0.67) | 0.0001 | 0.47 (0.34–0.66) | <0.0001 |

HR indicates hazard ratio; PACI, partial anterior circulation infarcts; TACI, total anterior circulation infarcts; POCI, posterior circulation infarcts; LACI, lacunar infarcts.

*For each 10-year increase of age.

and high prevalence of female gender (60.9%).[3,4,7,8,13,17,18] As a consequence, because the proportion of elderly women is increasing in many Western populations, the prevalence of AF will further increase.[3,19] Variations in the electrophysiologic structure of the heart and in the hormonal modulation of ionic channel function might explain the high prevalence of AF in elderly women.[19] Recent advances in understanding the pathophysiology of the disease might help to identify new strategies to prevent the development of the arrhythmia, especially in elderly women.[4]

In our population-based study, approximately one-fifth of all strokes is attributable to AF. Because ischemic stroke in patients with AF mostly depends on embolism, a primary preventive approach is mandatory,[4,7] considering that, so far, older people were less likely to be treated with oral anticoagulants for concerns linked to the risk of bleedings.[7,20] In the present study, only 11.3% of patients with AF were prescribed oral anticoagulants after the index event, irrespective of stroke type, mostly because of their contraindication during the acute phase. However, as suggested by the increasing prevalence of AF in the older age groups and by the increasing proportion of elderly subjects at risk in the general population, more widespread preventive measures should be recommended, even up to the oldest ages.[4,7,20]

In our study the proportion of patients with paroxysmal AF was low (6.3%).[15] For this reason, our findings mostly apply to patients with chronic AF. Because the stroke risk is likely to increase whenever paroxysmal AF becomes chronic, possible predictors of such occurrence should be identified to apply prophylactic measures.[21–23] Valvular AF occurred in 7.0% of mostly young patients, in agreement with the decreasing relevance of rheumatic fever in Western populations.[6,8] The 10.2% of patients with lone or idiopathic AF suggests that genetic and molecular mechanisms might be involved in the development of the arrhythmia.[17,18]

Among patients with AF, we found a high prevalence of coronary heart disease and peripheral arterial disease, confirming that in older patients AF is often associated with an underlying cardiovascular pathology.[3,4,22,24] Thus, accurate control of vascular risk factors should be recommended, even though the prevalence of cigarette smoking and hypercholesterolemia was low, probably as a consequence of selective survival and lifestyle changes.

The 30-day case-fatality rate of patients with AF (32.5%) was higher than previously reported (17% to 25%),[3,4,8,18,25] whereas the 1-year rate (49.5%) was within a wider range (30.5% to 63%).[20,26,27] At the Cox regression analysis, AF emerged as an independent predictor of mortality even after adjusting for other outcome predictors, suggesting that with appropriate prevention and treatment of AF the death risk of stroke patients might be reduced.[8,18,22,25]

In patients with AF with respect to patients without the arrhythmia, case-fatality rates were almost doubled, whereas the long-term survival was worse.[3,4,20] The poorer long-term prognosis of patients with AF might have depended on the increased recurrence rate that we observed in the same patients after 1 year of follow-up.[3,4,20,28] However, because the Cox regression analysis did not confirm the higher risk of stroke recurrence in patients with the arrhythmia, general frailty of elderly subjects with AF was more likely responsible for the observed high mortality during the long-term follow-up.

Overall, in our cohort, 17% of all deaths that occurred within 1 year from the index event were attributable to the presence of AF. Because stroke lethality is higher in older persons, the difference in mortality between subjects with and

without AF is likely to become progressively more evident as populations get older, suggesting that treating AF is crucial to reduce stroke mortality, probably preferring rate to rhythm control.[3,7,19]

In conclusion, in our population-based study, AF is a major contributor to stroke incidence and a powerful predictor of mortality after a first-ever ischemic stroke. However, even if better control of vascular risk factors together with a wider use of oral anticoagulants or antiplatelet agents might contribute to reduce stroke risk and mortality in patients with AF, new strategies are needed to prevent the development of the arrhythmia, especially in elderly women.

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