# Characteristics, Outcome, and Care of Stroke Associated With Atrial Fibrillation in Europe: Data From a Multicenter Multinational Hospital–Based Registry (The European Community Stroke Project)

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# Characteristics, Outcome, and Care of Stroke Associated With Atrial Fibrillation in Europe

## Data From a Multicenter Multinational Hospital–Based Registry (The European Community Stroke Project)

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***Background and Purpose***—The role of atrial fibrillation (AF) as a determinant of stroke outcome is not well established. Studies focusing on this topic relied on relatively small samples of patients, scarcely representative of the older age groups. We aimed at evaluating clinical characteristics, care, and outcome of stroke associated with AF in a large European sample.

***Methods***—In a European Concerted Action involving 7 countries, 4462 patients hospitalized for first-in-a-lifetime stroke were evaluated for demographics, risk factors, clinical presentation, resource use, and 3-month survival, disability (Barthel Index), and handicap (Rankin scale).

***Results***—AF was present in 803 patients (18.0%). AF patients, compared with those without AF, were older, were more frequently female, and more often had experienced a previous myocardial infarction; they were less often diabetics, alcohol consumers, and smokers (all $P<0.001$). At 3 months, 32.8% of the AF patients were dead compared with 19.9% of the non-AF patients ($P<0.001$). With control for baseline variables, AF increased by almost 50% the probability of remaining disabled (multivariate odds ratio 1.43, 95% CI 1.13 to 1.80) or handicapped (multivariate odds ratio 1.51, 95% CI 1.13 to 2.02). Before stroke, only 8.4% of AF patients were on anticoagulants. The chance of being anticoagulated was reduced by 4% per year of increasing age. AF patients underwent CT scan and other diagnostic procedures less frequently and received less physiotherapy or occupational therapy.

***Conclusions***—Stroke associated with AF has a poor prognosis in terms of death and function. Prevention and care of stroke with AF is a major challenge for European health systems. **(*Stroke*. 2001;32:392-398.)**

**Key Words:** atrial fibrillation ■ prognosis ■ stroke management ■ stroke outcome ■ stroke prevention

Among persistent cardiac arrhythmias, atrial fibrillation (AF) is the most frequent in clinical practice.[1] The overall frequency in the general population approaches 0.9%, and >2 million people are estimated to be affected in the United States.[2] The prevalence of AF is age dependent, rising from ≈1% among individuals aged 55 to 59 years to >13% among those aged ≥80 years.[3]

AF has been identified as an important cause of death in the elderly and a powerful risk factor for stroke.[4–7] AF has also been reported to be one of the major contributing factors in hospital expenditures for the care of acute stroke.[8]

Despite the noncontroversial evidence about its pathogenic role, whether or not AF is an independent determinant of stroke outcome has not been conclusively established. Studies examining AF as an independent predictor of death, disability, or stroke recurrence have been based on relatively small samples of patients, especially in the older age groups.[6,9–13]

The aim of the present study was to evaluate, in a large sample of patients hospitalized for first acute stroke in Europe, characteristics and outcome of the stroke event associated with AF. Selective aspects of the care provided to the patient with this type of stroke were also examined.

## Subjects and Methods

A European Union BIOMED Concerted Action was initiated to establish the relationships between resource use, costs, and outcome of packages of care for stroke in Europe. The specific objectives have been outlined previously.[14,15] The study involved 12 centers (22 hospitals) in 7 European countries: England, France, Germany,

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Hungary, Italy, Portugal, and Spain. All the hospitals provide general acute care to the local population; most are community hospitals serving up to 150 000 inhabitants and, overall, cover urban, suburban, and rural areas. Some centers, located in the United Kingdom, Germany, Hungary, and Italy, have acute stroke–monitoring facilities. In the majority of the centers, patient-based data collection began in September 1993, and all first-ever strokes admitted during the subsequent year were registered. Informed consent was given according to institutional rules. Stroke was defined according to the World Health Organization.[16] The study variables were chosen after an initial workshop attended by the study participants, who were all involved in stroke research and in the establishment of stroke registers.[17,18] The variables were similar to those used in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Stroke Study.[19]

Stroke-specific data forms were prepared, and information was gathered by dedicated data collectors in each center. Patients were evaluated in the acute phase and 3 months after the stroke. A detailed description of all study variables is provided elsewhere.[15] The present study compared, among all stroke patients registered, 2 subsamples of patients, those with and those without AF. The following variables were examined:

1. Baseline characteristics: age, sex, living conditions (living at home or in an institution), drug usage before stroke (antihypertensive, antiplatelet, and anticoagulant therapy), and prestroke level of handicap, as defined by the modified Rankin Scale.[20]

2. Vascular risk factors and comorbid conditions: hypertension (previous diagnosis, current treatment, or values >160/95 mm Hg in at least 2 subsequent measurements), AF (history of chronic AF supported by past ECG and positive ECG for the arrhythmia during hospitalization or past medical history supported by positive ECG during hospitalization), previous myocardial infarction, transient ischemic attack (TIA; acute neurological deficit of vascular origin, lasting <24 hours), diabetes mellitus (previous diagnosis or concurrent treatment with insulin or oral hypoglycemic medications or fasting glucose level of ≥7.8 mmol/L [≥140 mg/dL]), smoking (current or former practice), and alcohol consumption.

3. Clinical condition at time of maximum impairment within the first 7 days: level of consciousness (subsequently dichotomized into 2 categories of coma or noncoma),[21] confusion during the first week after the stroke, presence and site of weakness or paralysis, speech or swallowing problems as a result of stroke, and urinary incontinence.

4. Use of major diagnostic tests (brain imaging, angiography, Doppler sonography, or echocardiogram) or therapeutic interventions (neurosurgery, carotid surgery, or other vascular surgery) and amount of inpatient rehabilitation (formal therapy session performed by trained therapist: physiotherapy, occupational therapy, and speech therapy).

5. Destination from acute hospital: home, rehabilitation hospital, or institution.

Pathological types of stroke were as follows: cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and unclassifiable stroke, distinguished by the results of brain imaging. By use of the clinical criteria proposed by the Oxfordshire Community Stroke Project,[22] subtypes of ischemic stroke were rated into total anterior circulation infarct, partial anterior circulation infarct, posterior circulation infarct, and lacunar infarct.

Outcome data were collected 3 months after stroke onset. These included information on vital status, ability to perform activities of daily living as measured by the Barthel Index,[23] and handicap assessed by the Rankin scale. These assessments were usually made through a direct or a proxy face-to-face interview, except at 1 UK center, where, for follow-up, a previously validated postal questionnaire was used. Additional information was obtained from case notes and other routine hospital and general practice sources. In case of death, the date and cause were registered from information gathered from relatives or general practitioners.

To minimize variability across centers and between different observers, a manual was produced outlining the definitions of each data item. The study team visited each center to oversee data collection. Issues regarding the collection, interpretation, and quality of the data were discussed at site visits and at 6 monthly meetings of the study group.

## Statistical Analysis

Analysis of the differences in the frequency of categorical variables was carried out by using the $\chi^2$ test; the Student *t* test for independent samples was used for the continuous variables. The role of AF as an independent predictor of the clinical presentation was evaluated in a series of forward stepwise logistic regression analyses, taking into account all baseline variables and controlling for demographics and prestroke level of handicap.

Disability and handicap were evaluated according to the Barthel Index and the Rankin scale, the categories of which form an ordinal scale. Previous observations on the validity of statistical methods for the analysis of stroke outcome emphasized that intervals among points are not necessarily equal in these scales and, therefore, that it would be more appropriate not to analyze them as continuous variables.[24] The other options were to use nonparametric tests or to categorize patients into 2 groups, dichotomizing the scales and expressing the results as odds ratios (ORs) estimated by logistic regression analysis. Consequently, the Barthel Index and the Rankin scale were evaluated by univariate analysis with use of the Mann-Whitney nonparametric test and, subsequently, by a logistic regression analysis. By dichotomizing both scales, we were able to better estimate the net effect of the predictive variables on the transition from total or nearly total independence to limitation in daily functioning. The selected categories were 0 to 14 and 15 to 20 for the Barthel Index and 0 to 1 and 2 to 5 for the Rankin scale.

Outcome measures were death, disability, and handicap. Logistic regression analysis, with a forward stepwise method for selection of variables, was used to identify, among baseline variables, the role of AF as an independent predictor of 3-month outcome. This analysis was subsequently extended with the progressive inclusion of acute-phase variables in a series of multivariate models. All analyses were controlled for age and sex, and the models for handicap were also controlled for the prestroke level of handicap.

All statistical levels quoted (probability values) are 2-tailed. The 95% CIs were calculated to describe the precision of the estimates. Data were analyzed by use of the SPSS statistical software.[25]

# Results

During the 12-month study period, 4534 consecutive patients with a first-in-a-lifetime stroke were registered in the participating hospitals, and 4462 (50.2% females; mean age 71.8±12.6 years, range 13.7 to 102.1 years; and 1347 aged ≥80 years) completed the data set. AF was found in 803 (18.0%) of the patients (57.9% females). In the whole sample, the frequency of AF increased from 3.8% in patients aged <50 years to 34.3% in those aged ≥90. When prestroke characteristics were compared (Table 1), patients with AF were older and more often female, and they reported more frequently a history of myocardial infarction and showed a higher prestroke level of handicap, as defined by the Rankin scale. Diabetes, alcohol consumption, and smoking were more common among patients without AF. History of hypertension and previous TIA did not differ between the 2 groups.

The clinical conditions at the time of maximum impairment were more severely compromised in patients with AF, who (compared with patients without AF) were more often confused or in a coma and presented with paralysis, language deficits, swallowing problems, and urinary incontinence more frequently (Table 2).

**TABLE 1. Baseline Characteristics of Patients by Presence of AF**

| Variable | AF | | | Total Sample (n=4462) |
|---|---|---|---|---|
| | Yes (n=803) | No (n=3659) | *P* | |
| Mean±SD age, y | 77.3±9.6 | 70.6±12.9 | <0.001 | 71.8±12.6 |
| Sex (female) | 57.9% | 48.5% | <0.001 | 50.2% |
| Hypertension | 49.5% | 48.4% | 0.589 | 48.6% |
| Diabetes | 17.3% | 21.7% | 0.006 | 20.9% |
| Alcohol | 29.5% | 35.6% | 0.002 | 34.5% |
| Smoking | 29.2% | 39.6% | <0.001 | 37.7% |
| Previous myocardial infarction | 14.1% | 10.2% | 0.002 | 10.9% |
| Previous TIA | 13.7% | 12.2% | 0.270 | 12.5% |
| Baseline Rankin score (2–5) | 33.6% | 25.8% | <0.001* | 27.2% |
| Before stroke institutionalization | 7.2% | 5.5% | 0.062 | 5.8% |

*Mann-Whitney test.

Table 3 shows the distribution of pathological types of stroke according to the presence or the absence of AF. No difference was observed for ischemic stroke. Cerebral or subarachnoid hemorrhages were diagnosed more often in non-AF patients, whereas stroke was more frequently judged unclassifiable in AF patients. This was mostly explained by the less frequent use of brain imaging in this latter group. The classification into ischemic stroke subtypes according to the Oxfordshire Community Stroke Project criteria was available for 2462 (90.1%) of the 2731 ischemic stroke events. Patients with AF had total anterior circulation infarct and partial anterior circulation infarct more frequently and lacunar infarct less frequently.

In a series of multivariate analyses controlling for demographics, prestroke Rankin score, and all baseline risk factors, AF was still a significant predictor of confusion (OR 1.41, 95% CI 1.17 to 1.70), coma (OR 1.74, 95% CI 1.32 to 2.30), paralysis (OR 1.66, 95% CI 1.39 to 1.98), aphasia (OR 1.51, 95% CI 1.27 to 1.80), swallowing problems (OR 1.88, 95% CI 1.56 to 2.25), and urinary incontinence (OR 1.64, 95% CI 1.38 to 1.96). Moreover, AF was strongly associated with the diagnosis of total anterior circulation infarct (OR 1.59, 95% CI 1.26 to 2.01) and negatively associated with the diagnosis of lacunar infarct (OR 0.48, 95% CI 0.36 to 0.63).

**TABLE 2. Clinical State at Time of Maximum Impairment Among Patients With and Without AF**

| Variable | AF | | | Total Sample (n=4462) |
|---|---|---|---|---|
| | Yes (n=803) | No (n=3659) | *P* | |
| Confusion | 39.0% | 27.6% | <0.001 | 29.6% |
| Coma | 12.3% | 7.6% | <0.001 | 8.4% |
| Paralysis | 51.4% | 36.6% | <0.001 | 39.3% |
| Aphasia | 41.8% | 30.3% | <0.001 | 32.4% |
| Dysarthria | 35.0% | 33.2% | 0.319 | 33.5% |
| Swallowing problems | 40.3% | 23.6% | <0.001 | 26.6% |
| Urinary incontinence | 54.6% | 38.7% | <0.001 | 41.5% |

Laboratory investigations, such as brain imaging, Doppler examination, and angiography, were performed less frequently in patients with AF. Only the use of echocardiogram was more common in AF patients. The percentage of patients receiving physiotherapy or speech therapy was similar when the 2 groups were compared, but a significantly lower proportion of patients with AF received occupational therapy. Increasing age was relevant for the chance of receiving brain imaging or angiography (Table 4). Moreover, patients with AF received a lower number of physiotherapy and occupational therapy sessions (7.9±10.9 versus 9.0±13.3 for non-AF patients [$P=0.048$] and 1.5±4.6 versus 2.9±7.7 for non-AF patients [$P<0.001$], respectively). The difference in the mean number of speech therapy sessions was not significant (2.1±5.5 for AF versus 2.2±6.4 for non-AF patients, $P=0.539$).

The 28-day mortality was 19.1% among AF patients and 12.0% in the non-AF group ($P<0.001$), similar to the total in-hospital mortality (19.0% and 12.7%, respectively; $P<0.001$). The length of hospital stay did not differ between the 2 groups (23.9±26.6 versus 22.7±24.8 days, $P=0.264$). Patients with AF were significantly less often discharged home (61.4% versus 71.4%, $P<0.001$) and were more often referred to an institution (9.2% versus 6.1%, $P=0.003$). There was no difference in the proportion moved to a rehabilitation hospital (9.9% of the AF patients versus 8.7% of non-AF group, $P=0.334$).

Follow-up data were available for 3504 patients (78.5% of the total study sample [79.6% in the group with AF and 78.3% in the group without AF]). At 3 months, 32.8% of the patients with AF were dead compared with 19.9% in the non-AF group ($P<0.001$). Among survivors at 3 months, the mean Barthel Index was 12.8±7.2 in the AF group versus 15.3±6.2 in the non-AF group ($P<0.001$, Mann-Whitney test). The mean Rankin score was 2.7±1.6 in the AF group versus 2.3±1.5 in the non-AF group ($P<0.001$, Mann-Whitney test).

With control by logistic regression analysis for age, sex, and all other baseline variables (prestroke handicap included),

**TABLE 3. Stroke Pathological Types and Clinical Syndromes of Ischemic Stroke in Patients With and Without AF**

| | AF | | | |
|---|---|---|---|---|
| Variable | Yes | No | *P* | Total Sample |
| Stroke type, n | 803 | 3659 | | 4462 |
| Cerebral infarction | 61.6% | 61.1% | 0.778 | 61.2% |
| Cerebral hemorrhage | 6.0% | 11.4% | <0.001 | 10.4% |
| Subarachnoid hemorrhage | 0.4% | 2.1% | <0.001 | 1.8% |
| Unclassifiable | 32.0% | 25.4% | <0.001 | 26.6% |
| Clinical syndromes of ischemic stroke, n | 470 | 1992 | | 2462 |
| Total anterior circulation infarct | 33.8% | 25.1% | <0.001 | 26.7% |
| Partial anterior circulation infarct | 34.7% | 28.7% | 0.011 | 29.9% |
| Posterior circulation infarct | 15.5% | 17.0% | 0.437 | 16.7% |
| Lacunar infarct | 16.0% | 29.2% | <0.001 | 26.7% |

AF independently predicted 3-month death (multivariate OR 1.57, 95% CI 1.29 to 1.90). Similar results were obtained when AF was analyzed as a determinant of 3-month handicap, defined as a Rankin score >1 (multivariate OR 1.51, 95% CI 1.13 to 2.02). When acute-phase variables were added sequentially to the multiple regression models, the effect of AF on 3-month death and handicap progressively weakened and became nonsignificant after the inclusion of swallowing problems, paralysis, and coma. This indicates that the effect of AF on the outcome is confounded by stroke severity. AF was also the best predictor of 3-month disability when only baseline variables were considered (OR 1.43, 95% CI 1.13 to 1.80), becoming nonsignificant when acute-phase variables were added to the models.

Because the data had been collected by several centers across Europe, a control of the prediction of stroke outcome by AF for the effect of the different national settings in which the patients had been enrolled was found advisable. After the variable country was added to the multivariate models analyzing the predictors of death and functional outcome, the effect of AF was confirmed. Despite the different types of hospitals and the different care procedures, the greater severity of stroke associated with AF was confirmed in every participating center. Death at 28 days and 3 months was more common among stroke patients with AF across all countries. Patients who were severely disabled at 3 months were also more frequent in the AF group in all countries, except UK and Portugal. Our database provided information about the proportion of patients with AF who were treated with antithrombotic drugs (antiplatelet or anticoagulant therapy) before stroke. This may be regarded as an approximate indication of the use of these therapies for stroke prevention in patients with AF, both in the entire European sample and in the single countries. In the entire sample, antiplatelet therapy was used in 26% of AF patients, and anticoagulant therapy was used in only 8.4%. The percentage of patients with AF treated before stroke with antiplatelet therapy ranged (across the participating countries) from 39% in France to 18% in Portugal. The percentage of those treated with anticoagulants was 4.5% in Germany, 4.7% in Portugal, 7.8% in Italy, 9.5% in Hungary, 10.1% in UK, 11.1% in Spain, and 18% in France. We evaluated, at first by univariate analysis and afterward by a logistic

**TABLE 4. Resource Use During Hospitalization by Presence of AF**

| | AF | | | | |
|---|---|---|---|---|---|
| Variable | Yes (n=803) | No (n=3659) | *P* | *P** | Total Sample (n=4462) |
| Brain imaging | 77.4% | 82.3% | 0.001 | 0.506 | 81.4% |
| Doppler | 28.2% | 40.8% | <0.001 | 0.012 | 38.6% |
| Echocardiogram | 31.2% | 25.8% | 0.002 | <0.001 | 26.8% |
| Angiography | 3.0% | 8.5% | <0.001 | 0.078 | 7.5% |
| Neurosurgery | 0.3% | 3.7% | <0.001 | 0.004 | 3.1% |
| Carotid surgery | 0.4% | 1.0% | 0.075 | 0.146 | 0.9% |
| Other vascular surgery | 0.3% | 0.6% | 0.249 | 0.533 | 0.5% |
| Physiotherapy | 63.5% | 65.2% | 0.373 | 0.526 | 64.9% |
| Speech therapy | 23.3% | 23.4% | 0.961 | 0.776 | 23.4% |
| Occupational therapy | 18.8% | 24.7% | 0.002 | 0.027 | 23.6% |

*Adjusted for age.

regression model, the variable country together with age, sex, history of hypertension, diabetes, alcohol intake, smoking, prior myocardial infarction, TIA, living alone, living in an institution, and degree of handicap before stroke as potential predictors for AF patients of being on anticoagulants or not. Although in the univariate analysis, the country turned out to be significantly associated ($P=0.024$) with anticoagulant treatment, together with younger age ($P<0.001$) and history of TIA ($P=0.029$), in the multivariate model, the only significant determinant remaining was age: the multivariate OR was 0.96 (95% CI 0.93 to 0.99) for the probability of being treated with anticoagulants before stroke per each increasing year of age. Accordingly, the proportion of patients with AF receiving anticoagulant therapy was 23.1% in the group aged <60 years, 9.6% in the group aged 60 to 79 years, and only 5.4% among patients aged ≥80 years ($P<0.001$ for trend).

## Discussion

The data come from a large European hospital setting involving 22 units in 12 centers in 7 European countries. Although these hospitals might not necessarily be representative of their entire country, with urban and rural population coverage and predictable variations of services among the hospitals, the information may reflect characteristics of stroke and stroke care practiced in western and central Europe. However, hospitalization rates for stroke may differ across various countries and may be biased toward younger patients and more severe events.[12]

Our rate of patients lost to follow-up (21.5%) is similar to that reported by large studies on stroke outcome.[26–28] Between the 2 study groups, those with and those without AF, no differences were observed in the percentage of patients who had been followed up. The chance of being lost to follow-up was higher for younger patients compared with older patients (mean age 72.6±12.1 years among those followed up versus 69.1±13.9 among those lost to follow-up, $P<0.001$) and for those without major neurological deficits. Accordingly, the rate was low for patients with AF. This could have caused an overestimation of the effect of AF on stroke outcome.

In Europe, stroke associated with AF accounts for almost one fifth of the patients hospitalized for acute stroke, in keeping with reported figures ranging from 15% to 23%.[9–12,29–31] Patients with stroke and AF are predominantly old and female and, compared with patients without AF, have less conventional risk factors for stroke. Stroke associated with AF is severe and has a poor prognosis regarding both 28-day and 3-month mortality, residual disability, and handicap and the type of destination after discharge (institution rather than home). AF increases the risk of death, disability, and handicap at 3 months by ≈50%, independent of other baseline risk factors.

Despite the more severe clinical presentation, brain imaging and other diagnostic procedures are used in Europe less often in AF patients than in non-AF patients. This attitude was partly dependent on age. From the present study, we have already reported a negative correlation between age and the probability of receiving brain imaging.[32]

The proportion of patients with stroke and AF admitted to the study hospitals that were or were not on anticoagulants has to be considered a biased indicator of routine utilization of anticoagulants for stroke prevention in the population served by each hospital. Given the known efficacy of anticoagulants, the untreated compared with the treated patients with AF have a greater chance of being admitted to a hospital after a stroke. However, several studies conducted in different geographical areas[33,34] have consistently reported that in the general population, only a minority of patients with AF are treated with anticoagulants for stroke prevention. Therefore, albeit approximately, we can assume the proportion of stroke patients with AF pretreated or not with anticoagulants to be an indicator of anticoagulant use in the different geographical settings.

In our European sample, the 8.4% (range 4% to 18% across the different centers) of patients with AF being anticoagulated before stroke appears to be a negligible proportion, considering the strength of evidence on anticoagulation for stroke prevention in patients with AF,[35] despite recent data suggesting that many patients with AF do not substantially benefit from anticoagulation treatment.[36] The presence or absence of risk factors such as hypertension and diabetes, considered to contribute to risk stratification in patients with AF,[36] did not alter the prediction of anticoagulant treatment. For stroke patients with AF, increasing age was the only independent determinant (among a number of putative predictors) of not being on anticoagulants. Age difference explained most of the variability observed across different countries in the anticoagulation treatment. Considering that the incidence of stroke associated with AF increases with aging and that the very old are those bearing the major burden of this type of stroke,[37–40] the decreasing chance of being anticoagulated with increasing age appears paradoxical. However, caution is claimed by many concerning the safety of anticoagulation in elderly patients with AF.[41] Development of safer antithrombotic therapies for stroke prevention in older patients with AF may be a valuable task for pharmacological and clinical research in the forthcoming years.[42,43]

Considering the demographic transition, we can expect in the future a progressive increase in the burden on European health systems that is consequent to strokes occurring in subjects with AF. When the severity of this type of stroke, its poor outcome, and the unsatisfactory application of randomized controlled trials results are taken into account, reducing the burden of stroke associated with AF must be one of the major challenges facing health planning in Europe in the next decades.

## Appendix

### Study Participants

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