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# Non-permanent atrial fibrillation and oral anticoagulant therapy are related to survival during 10 years after first-ever ischemic stroke

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ABSTRACT

*Background:* Atrial fibrillation (AF) detection in ischemic stroke patients triggers initiation of oral anticoagulant therapy (OAC). However, little is known regarding whether the persistency of AF affects long-term prognosis after ischemic stroke. We aimed to assess the impact of AF types and OAC on the outcome during a 10-year follow-up (FU) after first-ever ischemic stroke.
*Material and methods:* The study sample comprised 336 first-ever ischemic stroke patients (median age 76, interquartile range 25–75% (IQR) 67–82 years, 136 female) included in the Lund Stroke Register (LSR) in 2001–2002. At baseline, 109 patients had either permanent (n = 44) or recurrent (n = 65) AF. OAC was assessed using the Lund University Hospital anticoagulation database. All-cause mortality was assessed via linkage with the Swedish Causes of Death Register.
*Results:* During FU, 200 patients died. AF independently predicted all-cause mortality (hazard ratio (HR) 1.52 95% CI 1.14–2.04, p = 0.005); the worst prognosis was observed for permanent AF (HR 1.86 95% CI 1.29–2.69, p = 0.001). Patients with recurrent AF receiving OAC had similar survival rates to patients without AF (HR 0.73 95% CI 0.38–1.39, p = 0.333), while prognosis was worst for patients with permanent AF without OAC (HR 2.28 95% CI 1.38–3.77, p = 0.001) and intermediate for patients with permanent AF on OAC (HR 1.57 95% CI 0.92–2.67, p = 0.099).
*Conclusion:* All-cause mortality was independently associated with AF and was the greatest in stroke patients with permanent AF. Patients with recurrent AF receiving OAC have the most favorable outcome, similar to those without AF and significantly better than OAC-treated patients with permanent AF.


## 1. Introduction

Atrial fibrillation (AF) is an established risk factor for ischemic stroke [1]. Most studies on AF in ischemic stroke patients are focused on detecting AF after ischemic stroke because detection of AF is crucial for initiating secondary prevention therapy regardless of clinical types of AF. It has been shown that the incidence of ischemic stroke is similar in patients with permanent AF and with paroxysmal AF [2]. Several studies demonstrated that patients with paroxysmal AF have less severe strokes than patients with chronic AF [3,4]. However, little is known about the impact of different clinical types of AF on long-term prognosis after ischemic stroke. While the benefit of anticoagulation in patients with AF at high risk of thromboembolic events is proven [1], it is unclear whether there is a difference in prognosis between patients with paroxysmal AF receiving oral anticoagulation (OAC) and patients with permanent AF receiving OAC.

We aimed to assess the impact of different types of AF and OAC therapy on outcomes in first-ever ischemic stroke patients during a 10-year follow-up.

## 2. Materials and methods

### 2.1. Study cohort

The study sample comprised 336 first-ever ischemic stroke patients included in the Lund Stroke Register (LSR) between March 1, 2001 and February 28, 2002 (median age 76, IQR 67–82 years, 136 female). At baseline, 109 stroke patients had AF, which was

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detected using medical records, data from regional electronic ECG database, and by linkage with the Swedish National Patient Register as previously described [5]. We followed up all study subjects until October 17, 2011.

Informed consent was obtained from all participants at enrollment in the LSR. The Lund Regional Ethics Committee approved the study.

### 2.2. Baseline clinical characteristics and ascertainment of AF types

Medical records of all study subjects were analyzed for history of congestive heart failure (CHF), hypertension, diabetes mellitus, TIA and ischemic heart disease (IHD) prior to or at stroke onset or enrollment. Stroke severity was estimated using the National Institutes of Health Stroke Scale (NIHSS) [6]. For all study subjects, we evaluated the cardiovascular risk profile at stroke using $CHA_2DS_2$-VASc score [1]. The index ischemic stroke was included when the score was calculated.

AF clinical types were categorized as permanent AF or recurrent AF [7]. AF was defined as recurrent when the attending physician described it in the medical records as paroxysmal or persistent (with consecutive cardioversion), or when after ECG recordings with AF prior to enrollment in the LSR, sinus rhythm ECG was registered at inclusion in the study. Patients who had AF diagnosis in accordance with the Swedish National Patient Register and had sinus rhythm at admission were considered as having recurrent AF. Permanent AF was diagnosed in accordance with attending physician's judgment as documented in medical records, or when serial ECGs demonstrated arrhythmia without intervening sinus rhythm, including the ECG at admission [8].

### 2.3. Oral anticoagulation therapy

Non-vitamin K antagonist oral anticoagulants were not available at the time of enrollment in the LSR, so in our study OAC therapy was limited to the use of warfarin.

OAC therapy at any time prior to stroke and during 10-year follow-up was assessed using the Lund University Hospital anticoagulation database, which contains data for all patients in the local catchment area receiving OAC, including dates of beginning and terminating warfarin therapy, indication for OAC treatment, and INR data. In the present study, we assessed the beginning of OAC therapy, duration of treatment, the date of therapy termination and reasons of withdrawal for patients who were prescribed OAC.

### 2.4. End point and statistical methods

The end point in this study was all-cause mortality. Vital status, dates of death, and primary and secondary diagnoses on the date of death for all patients were determined via linkage with the Swedish Causes of Death Register (SCDR). SCDR is maintained by the Swedish National Board of Health and Welfare and contains information from 1961 to present day. The Register uses International Classification of Disease (ICD) codes, with the 10th edition (ICD-10) used starting in 1997 and until today [9,10]. The information is derived from death records, including underlying causes of death and up to 20 contributory causes of death coded to the current ICD edition at the time of death [11,12].

Baseline univariate comparison between stroke patients with different clinical types of AF was performed using chi-square or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables with an approximate normal distribution or non-parametric tests, as appropriate.

Patients who remained alive were censored at the end of follow-up. Survival status in relation to each component of $CHA_2DS_2$-VASc score was analyzed using univariate Cox regression analyses. Cox proportional hazard regression models were used to estimate the adjusted hazard ratios (HR) and their 95% confidence intervals (CI) of all-cause mortality associated with clinical covariates, such as age, gender, cardiac failure, hypertension, diabetes mellitus, vascular diseases and stroke severity. Clinical factors significantly associated with mortality in the univariate analyses were included in a stepwise regression analysis with backward elimination.

Logistic regression analysis was performed to evaluate odds ratios (OR) and 95% CI of the same clinical factors as in the Cox regression model that were associated with in-hospital mortality.

The impact of AF clinical types and OAC therapy on the outcome was evaluated using univariate Cox regression analysis and multivariate Cox regression analysis with backward elimination for significantly associated clinical factors. The Kaplan-Meier product-limit method was used to generate a survival curve indicating survival during the 10-year follow-up after the first-ever ischemic stroke.

p-Values of $<0.05$ were considered significant. All analyses were performed using SPSS Statistics 20 (SPSS Inc., Chicago, Illinois, USA).

## 3. Results

### 3.1. Predictors of all-cause mortality during long-term follow-up after first-ever ischemic stroke

The baseline characteristics of the study cohort are summarized in Table 1.

During follow-up, 200 (60%) of the 336 patients died, with median time from stroke to death being 3.3 years (IQR 0.9–6.3). All-cause mortality was independently associated with age (HR 1.08 95% CI 1.06–1.10, $p < 0.001$), cardiac failure (HR 1.65 95% CI 1.05–2.57, $p = 0.029$), stroke severity measured by NIHSS scale (HR 1.10 95% CI 1.08–1.12, $p < 0.001$) and atrial fibrillation at admission (HR 1.52 95% CI 1.14–2.04, $p = 0.005$).

### 3.2. Clinical types of AF and impact on mortality after first-ever ischemic stroke

At stroke admission, 44 patients (40%) had permanent AF and 65 patients (60%) had recurrent AF. Baseline clinical profile is presented in Table 2. Patients with permanent AF were older than patients with recurrent AF and did not differ in regard to other cardiovascular risk factors and stroke severity.

322 (96%) patients were discharged alive. Among 14 patients who died before discharge from hospital, 11 patients had AF: permanent AF in 4 patients and recurrent AF in 7 patients ($p = 1.000$), none of these patients was treated with OAC at admission. In multivariate logistic regression analysis after adjustment for age and clinical factors, only stroke severity measured by NIHSS scale (OR 1.17 95% CI 1.10–1.25, $p < 0.001$) and AF at admission (OR 4.98 95% CI 1.16–21.27, $p = 0.031$, for recurrent AF OR 5.23 95% CI 1.08–25.41, $p = 0.04$, for permanent AF OR 4.66 95% CI 0.84–25.02, $p = 0.078$) were independently associated with in-hospital mortality.

All-cause mortality during follow-up in multivariate Cox regression model was associated with AF at stroke admission (HR 1.52 95% CI 1.14–2.04, $p = 0.005$), and permanent AF was found to have the greatest impact on mortality (HR 1.86 95% CI 1.29–2.69, $p = 0.001$). A separation between the Kaplan-Meier survival curves for recurrent and permanent AF was observed after the 3rd year of follow-up (Fig. 1).

### 3.3. Oral coagulation therapy in stroke patients with AF

At stroke onset, 5 patients with permanent AF (11%) and 5 patients with recurrent AF (8%) were already on treatment with OAC, $p = 0.521$.

Among stroke patients with AF, 98 (90%) were discharged alive (40 with permanent AF and 58 with recurrent AF, $p = 1.000$); 38 of the patients (39%) were prescribed vitamin K antagonist warfarin: 18 patients with permanent AF (45%) and 20 patients with recurrent AF (35%), $p = 0.175$. Six more patients with recurrent AF (10%) were subsequently transferred from antiplatelet therapy to warfarin after discharge, with median time from stroke to initiation of OAC being 0.4 years (IQ 0.2–2.3 years). Baseline clinical characteristics of patients with different clinical types of AF receiving OAC compared with patients without OAC are presented in Table 3. Patients without OAC were significantly older than those treated with OAC.

In total, 44 stroke patients with AF (45%) received secondary prevention therapy during follow-up, with median time on OAC being

**Table 1**
Baseline clinical characteristics of stroke patients, n-336.

| Variable | |
|---|---|
| Female, n (%) | 136 (41) |
| Age, median (IQ) | 76 (67–82) |
| Age > 75 years, n (%) | 180 (54) |
| Cardiac failure, n(%) | 28 (8) |
| Hypertension, n (%) | 195 (58) |
| Diabetes mellitus, n (%) | 63 (19) |
| TIA, n (%) | 74 (22) |
| Vascular diseases, n (%) | 142 (42) |
| $CHA_2DS_2$-VASC, median (IQ) | 5 (4–6) |
| AF at baseline, n (%) | 109 (32) |
| Permanent AF, n (%) | 44 (13) |
| Reccurent AF, n (%) | 65 (19) |
| OAC therapy at enrollment, n (%) | 14 (4) |

TIA – transient ischemic attack.
IQ – interquartile range 25%–75%.
OAC – oral anticoagulant therapy.
AF – atrial fibrillation.

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