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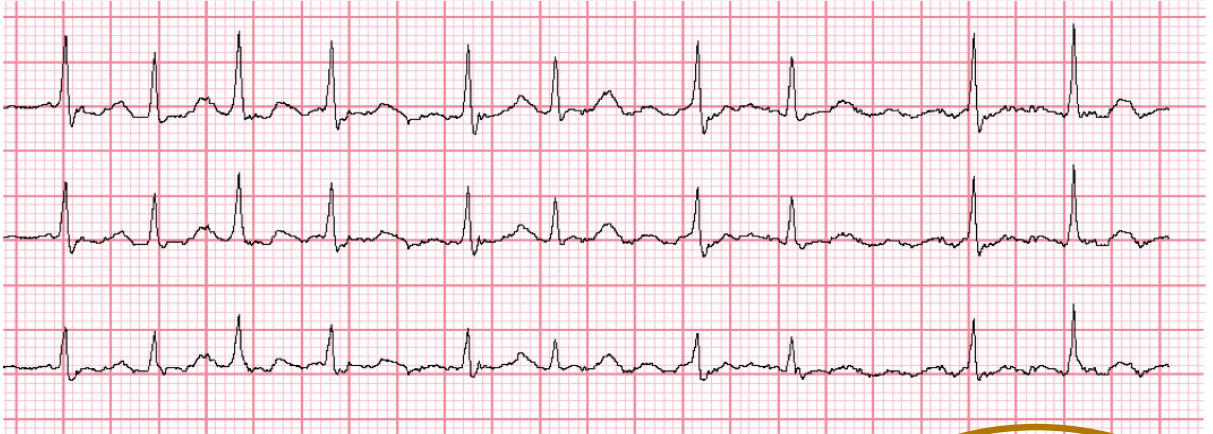
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Atrial fibrillation in ischemic stroke

Prevalence, long-term outcomes and secondary prevention therapy

MARIA BATUROVA

CARDIOLOGY DEPARTMENT, CLINICAL SCIENCES | LUND UNIVERSITY 2016



Atrial fibrillation in ischemic stroke

Atrial fibrillation in ischemic stroke:
Prevalence, long-term outcomes and
secondary prevention therapy

Maria Baturova



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DOCTORAL DISSERTATION

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May 13, 2016 at 09.00

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Professor Jens Cosedis Nielsen

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Title and subtitle: Atrial fibrillation in ischemic stroke: prevalence, long-term outcomes and secondary prevention therapy.		
<p>Abstract: Atrial fibrillation (AF) is a very-well known risk factor for ischemic stroke. The general aim of the study was to assess prevalence of AF in patients with first-ever ischemic stroke and to evaluate the impact of AF on outcomes during 10-year follow-up after the stroke event.</p> <p>The thesis consists of a retrospective register-based study and a <i>post hoc</i> analysis from the prospective case-control study. The main study population of patients with first-ever ischemic stroke (Study I, II, IV, V) was enrolled in the Lund Stroke Register during 2001-2002 and followed up for 10 years from date of enrollment. Patients treated with ischemic stroke at Mayo Clinic (Rochester, MN, USA) were prospectively included in the case-control study and underwent three-week ambulatory ECG monitoring for AF detection (Study III).</p> <p>For AF detection prior to stroke and during follow-up in the register-based study the combined approach was used with screening through regional electronic ECG archive and via linkage with the Swedish National Patient Register (Study I, IV), in which validity of the AF diagnosis was assessed against ECG documentation (Study II). Clinical, echocardiographic and electrocardiographic predictors of AF onset were evaluated using medical records and sinus rhythm ECG taken at stroke admission (Study III, IV). Oral anticoagulant therapy (OAC) was analyzed through Lund University Hospital anticoagulation database (Study I, V). All-cause mortality was assessed using the Cause of Death Register (Study V).</p> <p>Pre-stroke prevalence of AF appeared to be 32.4% and was associated with a high CHA₂DS₂-VASc score (Study I). In stroke patients, short runs of AF on prolonged ambulatory ECG monitoring were associated with increased left atrial volume index (Study III). A high CHA₂DS₂-VASc score predicted the development of AF during the 10 years following the first-ever ischemic stroke (Study IV). Permanent AF was associated with the worst prognosis, while the best prognosis during the 10-year follow-up was observed for ischemic stroke patients with recurrent atrial fibrillation treated with OAC (Study V). In conclusion, ischemic stroke patients with a high CHA₂DS₂-VASc score may be the target group for continuous AF screening and initiation of OAC therapy upon AF detection.</p>		
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In memory of my mother

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Manuscript

Abbreviations

AF – atrial fibrillation

ARIC – Atherosclerosis Risk in Communities Study

CT – computed tomography

EF – ejection fraction

ECG – electrocardiographic

ECHO – echocardiographic

FHS – Framingham Heart Study

HR – hazard ratio

IAB – interatrial block

ICD – International Classification of Disease

INR – international normalized ratio

IQR – interquartile range 25%-75%

LAVI – left atrial volume index

LSR – Lund Stroke Register

MR – magnetic resonance

NIHSS – National Institutes of Health Stroke Scale

NPV – negative predictive value

OAC – oral anticoagulant

OR – odds ratio

PPV – positive predictive value

ROC – receiver operating characteristic

STD – standard deviation

TTE – transthoracic echocardiography

Introduction

Atrial fibrillation is a risk factor for ischemic stroke

Cerebrovascular diseases are the leading cause of mortality in women and the second leading cause of death in men in industrialized countries (1). Stroke is the main reason of functional disability; one-third of all stroke survivors will not be able to resume their daily activities at the same level as before the stroke (2). Of all ischemic stroke subtypes, cardioembolic stroke is considered to be more severe; patients with cardioembolic strokes have a higher incidence of recurrent strokes as well as higher mortality (3). One of the leading causes of cardioembolic stroke is atrial fibrillation (AF) (4).

AF is the most common cardiac arrhythmia in the general population, with a prevalence of at least 3% (5), increasing with age and reaching 15% at 80 years (6). Patients with AF are at a higher risk of stroke, and one in five of all strokes is attributed to AF (6). AF in stroke patients confers an increased risk of morbidity and mortality as compared to non-AF-related stroke patients (7).

The main mechanism of an AF-related stroke is considered to be a thrombus formation in the left atrium in condition of irregular contractility. When a blood clot is formed, it can be pumped out of the heart to the brain, leading to cerebral artery occlusion.

The increased risk of stroke in AF patients can be reduced with oral anticoagulant (OAC) therapy. It has been shown that warfarin therapy in AF patients significantly reduces the risk of stroke (8) and prevents the development of cardioembolic events. In accordance with the current guidelines for managing of AF, AF patients with a risk of thromboembolic events should be treated with OAC.

However, AF is often asymptomatic, and sometimes ischemic stroke may be the first clinical presentation of the underlying AF. It has been reported that at least one-third of patients with AF had asymptomatic AF (9). In patients with implantable devices, subclinical AF was quite common and was associated with an increased risk of stroke (10). AF documentation in stroke patients is crucial for initiation of OAC therapy, as patients with ischemic stroke have a higher risk of thromboembolism (6).

Electrocardiographic screening for atrial fibrillation in ischemic stroke

Detecting AF in ischemic stroke patients is a challenge due to its paroxysmal nature. The majority of studies to date focused on dedicated electrocardiographic (ECG) screening for AF after stroke. On standard ECG at admission with ischemic stroke, AF is documented in 20% - 25% of patients (7, 11). Additional repeated conventional snapshot ECG recordings after stroke onset appeared to increase AF detection rate by 1.4 - 6.7% (12-14). Diagnostic yield of 24-48 hour Holter ECG monitoring in patients with ischemic stroke and sinus rhythm at admission has been reported to be 1% - 6.4% (12, 14, 15) and could be increased to 12.5% if the ECG recordings were continued for one week (15). In stroke patients who underwent 30-day ambulatory autotriggered AF detection, AF was documented in 6-11% of cases (16, 17). Outpatient cardiac telemetry during 3-4 weeks of ECG monitoring in patients with cryptogenic stroke helps identify 17-20% of new AF cases (18, 19). The highest detection rate of AF in patients with cryptogenic stroke was reported for patients with implantable cardiac monitors and appeared to be 30% (20). While the superiority of this strategy for AF detection is obvious, its cost effectiveness is largely affected by properly selecting the patients who would benefit from continuous AF screening.

All noted ECG methods are aimed at detecting AF after a stroke event. The causal link between AF detected after ischemic stroke and occurrence of stroke is questionable. We cannot completely rule out the possibility of electrophysiological changes in the heart appearing as a consequence of ischemic stroke (21). AF detected prior to stroke is more likely a contributing cause of ischemic stroke. In patients with implantable devices it was shown that subclinical AF detected in 10% of patients during the first 3 months of the study was associated with an increased risk of stroke during follow-up (10). However, data on pre-stroke prevalence of AF and its causal link with ischemic stroke are sparse.

Atrial fibrillation diagnosis in national patient registers

In population-based studies, national discharge registers are commonly used as a simple data source for identifying clinical endpoints. Data from the Swedish Patient Register have been used in epidemiological studies to estimate AF prevalence, incidence and risk factors for ischemic stroke (5, 22, 23). In the RIKS-Stroke study, the prevalence of AF was assessed via linkage with the Swedish National Patient Register and by a self-reported questionnaire, and was found to be 30% (24).

Whether or not national registers provide complete and accurate information about disease prevalence remains unclear. In previous studies, high validity of the Swedish National Patient Register was reported for diagnosis of acute myocardial

infarction and congestive heart failure (25, 26), with lower reported validity for less severe diseases, such as hypertension and lipid disorders (27).

Literature data on AF diagnosis validity in national registers are sparse, and, to our knowledge, only one study assessed the validity of AF diagnosis in the Swedish National Patient Register (28). In that study, validity was shown to be high when estimated in a randomly selected sample of 100 patients with a register-based AF diagnosis, verified by ECG data or by information from medical records (28). However, there is insufficient information regarding the sensitivity of AF diagnosis contained in the Swedish Patient Register.

Clinical factors, electrocardiographic and echocardiographic characteristics associated with atrial fibrillation

Due to the comparatively low sensitivity of conventional Holter monitoring techniques for AF detection after stroke and the high cost of prolonged monitoring strategies, there is a need to find a simple and non-invasive approach to identifying patients who would benefit from AF screening.

Clinical factors: CHADS₂ and CHA₂DS₂-VASc scores

Clinical risk factors for AF development are well-known. It was shown that apart from valve disease and male gender, age, congestive heart failure, diabetes and hypertension were independently associated with AF (29, 30). Based on the same risk factors, the CHADS₂ scoring system (Figure 1) was derived in order to predict cardioembolic stroke risk in patients with non-valvular AF and to guide antithrombotic therapy (31).

Risk factor	Score
Cardiac failure	1
Hypertension	1
Age ≥ 75	1
Diabetes	1
Stroke	2

Figure 1.
CHADS₂ score.

The CHA₂DS₂-VASc (Figure 2) score was introduced in order to incorporate additional stroke risk factors associated with the female gender and vascular disease, and to achieve greater accuracy regarding age-related risk (32).

Risk factor	Score
Cardiac failure	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke	2
Vascular diseases	1
Age 65-74	1
Female gender	1

Figure 2.
CHA₂DS₂-VASc score.

CHADS₂ and the CHA₂DS₂-VASc scores identify patients at risk for developing stroke and thromboembolic events (6). The CHADS₂ and CHA₂DS₂-VASc scoring systems have also been shown to be useful in predicting the development of AF in different cohorts of patients (23, 33, 34). It has also been shown that high CHADS₂ and CHA₂DS₂-VASc scores predict new-onset AF in ischemic stroke patients during 15 months of post-stroke follow-up (35), and that a more severe cardiovascular risk profile measured by the CHADS₂ scale is associated with first-ever AF during the first 2 years after stroke (23). While these scoring systems were initially introduced in order to predict cardioembolic risk in patients with AF, they seem to be useful for predicting AF development in patients without AF after ischemic stroke.

Electrocardiographic characteristics: P-wave indices

P-wave duration is considered to be a non-invasive marker of atrial conduction and size. Its prolongation reflects atrial remodeling, predisposing a patient to AF occurrence. In the Framingham Heart Study, the prolongation of P-wave duration predicted AF development during long-term follow-up in an elderly community-based cohort (36). It has been shown that P-wave duration > 120 ms is associated with AF development in people aged 55 to 74 years during long-term follow-up (37). However, in patients with congestive heart failure and severe cardiovascular risk factors, P-wave duration was not predictive of new-onset AF, while abnormalities in P-wave morphology recorded from orthogonal leads in surface ECG were independently predictive of AF development (38).

Another marker of atrial abnormalities is P terminal force in lead V1. Sinus P-waves with biphasic morphology in the right precordial leads quantified as increase of the negative terminal force in lead V1 were predominately found in elderly patients (39) and in patients with a history of AF (40). The Atherosclerosis Risk in Communities study showed that P terminal force in lead V1 greater than $4000 \mu\text{V} \cdot \text{ms}$ was associated with an increased risk of AF (41). However, whether or not P-wave characteristics could help identify stroke patients with underlying AF is not entirely clear.

Echocardiographic characteristics associated with AF: Left atrial volume index

Left atrial dilatation evaluated by transthoracic echocardiography (TTE) (Figure 3) is a consequence of structural changes in the atrium leading to the development of AF.

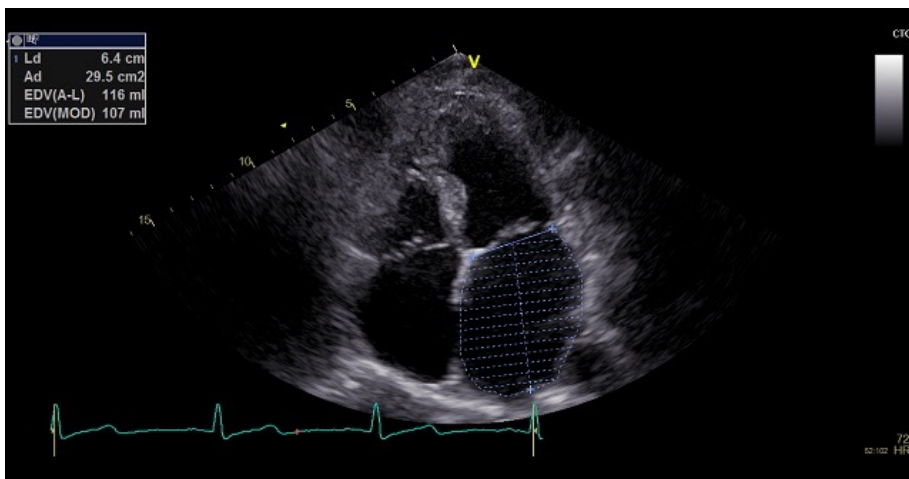


Figure 3. Increased left atrium on transthoracic echocardiography. Ld – length, Ad – area, EDV – volume.

Current guidelines for Cardiac Chamber Quantification by Echocardiography in Adults (42) recommend measuring left atrial volume index (LAVI) when assessing the left atrial size and remodeling.

Increased LAVI reflects remodeling of the left atrium due to pressure or volume overload (43) and correlates with the extent of left atrium fibrosis (44). Both atrial remodeling and atrial fibrosis are pathological changes underlying the development of AF. It has been shown that LAVI has a high diagnostic accuracy for paroxysmal AF in hypertensive patients (45). In ischemic stroke patients, LAVI was greater in patients with paroxysmal AF than in patients without AF (46). Increased LAVI may be a marker of underlying AF in ischemic stroke patients.

Clinical types of atrial fibrillation in ischemic stroke: prevalence, impact on outcomes and oral anticoagulant therapy

In accordance with the current guidelines for managing AF, five types of AF are distinguished:

First-diagnosed AF – newly diagnosed AF irrespective of arrhythmia duration or AF-related symptom severity;

Paroxysmal AF – self-terminating arrhythmia, usually within 48 hours, paroxysms may continue up to 7 days;

Persistent AF – AF episodes lasting longer than 7 days or requiring termination by cardioversion;

Long-standing persistent AF – AF lasting 1 year or more when it is decided by the patient and the attending physician to adopt a rhythm control strategy;

Permanent AF – AF exists when it is decided by the patient and the attending physician to adopt a rate control strategy.

Several studies reported that rate and rhythm control strategies had similar outcomes in regard to all-cause mortality, cerebrovascular complications and thromboembolic events (6). It is accepted that persistency of AF does not effect long-term prognosis if OAC therapy is administered. Recent reports suggested that ischemic stroke incidence appears to be similar in paroxysmal and permanent AF (47), and that paroxysmal AF carries thromboembolic complications risk similar to permanent AF (48).

However, there are contradictive literature data about the prevalence of different types of AF in ischemic stroke patients. Earlier, in patients with ischemic stroke it had been reported that the prevalent type of AF was permanent AF (7, 49, 50). Recent studies using dedicated AF screening measures after stroke contrary to above mentioned studies showed that the prevalent type of AF in stroke patients was paroxysmal AF (51, 52).

Though the incidence of ischemic stroke is similar in patients with permanent AF and paroxysmal AF, it has been shown that paroxysmal AF is associated with less severe strokes than permanent AF (49-51). A more favorable outcome has been demonstrated for paroxysmal AF compared with chronic AF at discharge after ischemic stroke (50) and higher in-hospital mortality was found in stroke patients with permanent AF compared to stroke patients with paroxysmal AF (53).

It was shown that AF presence at stroke onset was associated with the worst survival during long-term follow-up (7), however studies with focus on long-term prognosis after ischemic stroke usually disregard the type of AF.

In one study during 10-year follow-up after stroke it was demonstrated that paroxysmal AF was associated with the lower rates of stroke recurrence and mortality

than permanent and persistent AF (51). However, the literature data about the impact of different clinical types of AF on long-term prognosis after ischemic stroke are sparse.

The benefit of OAC therapy in patients with AF and risk of thromboembolic complications is well established (6, 54). However, it is unclear whether there is a difference in prognosis between OAC-treated patients with paroxysmal and permanent AF. A recently published subanalysis of the ROCKET-AF study (55), in which one third of patients had stroke in the past, reported that patients receiving anticoagulation with persistent AF have a higher risk of thromboembolic events and death compared to those with paroxysmal AF. Further studies are needed to clarify whether the efficacy of OAC is similar in patients with permanent AF and paroxysmal AF.

Aims

The overall objective of this thesis is to assess AF prevalence in patients with first-ever ischemic stroke and to evaluate the impact of AF on outcomes during 10-year follow-up after the stroke event.

The specific aims of the included papers were:

- To assess the pre-stroke prevalence and clinical types of AF in patients enrolled in the Lund Stroke Register (LSR) (Paper I).
- To evaluate the sensitivity and the specificity of AF diagnosis in the Swedish National Patient Register (Paper II).
- To find clinical risk factors, ECG and ECHO characteristics associated with AF detected after ischemic stroke using ambulatory 3-week ECG monitoring (Paper III).
- To estimate AF incidence and predictors of new-onset AF during 10 years of follow-up after first-ever ischemic stroke (Paper IV).
- To assess the impact of clinical types of AF and OAC on long-term prognosis after first-ever ischemic stroke (Paper V).

Material and methods

Study population

The thesis consists of a retrospective register-based study and a *post hoc* analysis from the prospective case-control study. The retrospective study (Study I, II, IV, V) is based on data collected in Lund through LSR. The *post hoc* analysis from the prospective case-control study (Study III) was performed in collaboration with Mayo Clinic, (Rochester, MN, USA) on ischemic stroke patients recruited in USA.

Lund Stroke Register

LSR is a prospective epidemiological register that covers the Lund University Hospital catchment area (8 municipalities with 234,505 inhabitants as of December 31, 2001) (56). LSR was administered in 2001. Patients with all first-ever-in-life strokes, including ischemic stroke, haemorrhagic stroke and subarachnoid haemorrhage were enrolled in the LSR when stroke was diagnosed in accordance with the World Health Organization definition (57) and confirmed by computed tomography (CT), magnetic resonance (MR) or autopsy examination of the brain. After the CT/MR/autopsy, the stroke was identified as ischemic stroke, haemorrhagic stroke or subarachnoid haemorrhage (58). Control subjects included in the LSR were randomly selected from the same geographical region and matched to stroke cases by age and gender in a 1:1 case-control manner using the Swedish Population Register (56).

Informed consent was obtained from all participants included in the LSR. The study was approved by the regional Ethics Committee.

The study sample was comprised of 336 first-ever ischemic stroke patients enrolled in the LSR during the first year (between March 1, 2001 and February 28, 2002) and 336 age- and gender-matched control subjects. All study subjects were followed up until October 17, 2011.

Study cohort from the prospective Mayo Clinic study

The study cohort was recruited from the cohort of ischemic stroke patients treated at Mayo Clinic (Rochester, MN, USA). Patients without history of AF or atrial flutter prior to or at the index stroke event were compared with those with documented paroxysmal AF at time of hospital admission with stroke.

The study group of patients without AF history was comprised of 110 patients with ischemic stroke – either cryptogenic (n=55) or of known cause (n=55) – who were

previously included in the recently published analysis (59) and who had a surface ECG during sinus rhythm obtained at stroke onset (mean age 67 ± 10 years, 40 female). Using ambulatory ECG monitoring for three weeks (Mobile Cardiac Outpatient Telemetry system - CardioNet, Conshohocken, PA, USA), short AF episodes of median 6-second duration (interquartile range 25%-75% (IQR) 6-9) were detected in 24 patients (22%). All arrhythmic episodes were manually reviewed by a board-certified electrophysiologist. The 24 patients with newly detected short AF episodes after stroke were compared to the 86 stroke patients without detected AF.

The control group was randomly selected from age- and gender-matched patients treated at Mayo Clinic with ischemic stroke who had a history of paroxysmal AF prior to stroke and sinus rhythm on standard 12-lead ECG at time of admission ($n=55$, 67 ± 10 years, 19 female).

The Mayo Clinic Institutional Review Board approved the research protocol.

Diagnosis and clinical types of atrial fibrillation

Information regarding AF presence prior to or at enrollment in the LSR was obtained from electronic medical records, ECG recordings retrieved from the regional electronic ECG database (GE MUSE, GE Healthcare) of the Scania region in southern Sweden, and by record linkage with the Swedish National Patient Register and Cause of Death Register. New-onset AF during the 10-year follow-up was assessed from the date of enrollment until the end of the follow-up period or until the date of death. AF documentation was based on information obtained from the regional electronic ECG archive and also by linkage with national registers: Swedish National Patient Register and Cause of Death Register.

Atrial fibrillation detection through electronic ECG archive

The regional ECG database contains all ECGs taken at the Skåne University Hospital, Lund catchment area, including primary care facilities, starting in 1988. All ECGs of ischemic stroke patients and control subjects recorded from 1988 until the end of follow-up were reviewed by a trained cardiologist (MB) for AF presence prior to ischemic stroke at enrollment in LSR and during the 10-year follow-up. A total of 7,247 ECG recordings were reviewed. On surface ECG, AF was defined as a rhythm disorder with irregular RR intervals, indistinct P-waves and atrial cycle length of < 200 ms in case of distinct atrial activity visible on surface ECG (Figure 4) (6). For statistical analysis purposes, atrial flutter was considered equal to AF.

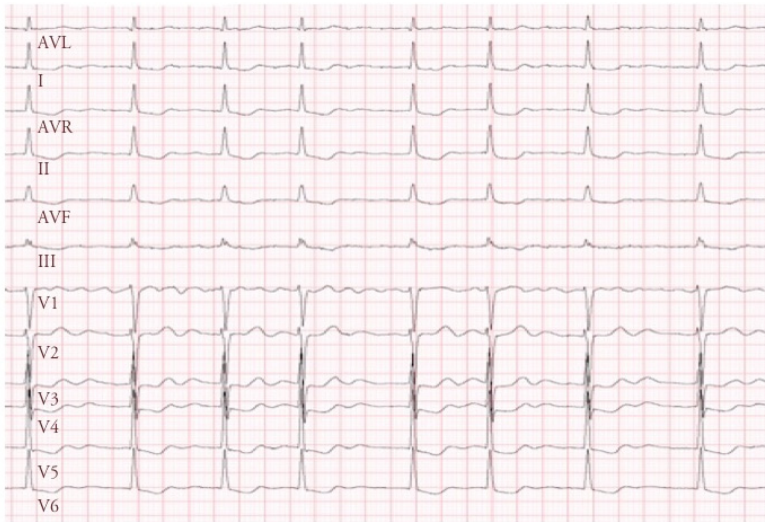


Figure 4.
ECG in 12 leads with AF from the regional electronic ECG archive.

Atrial fibrillation detection by record linkage with national registers

The Swedish Patient Register is administered by the Swedish National Board of Health and Welfare and includes data on primary and secondary diagnoses at discharge from all public hospitals in Sweden starting in the year 1987. The Swedish Patient Register also includes information regarding outpatient hospital visits. All diagnoses are reported by physicians. The register uses International Classification of Disease (ICD) codes, with the 9th edition (ICD-9) used between 1987 and 1996 and the 10th edition (ICD-10) used starting in 1997 and until today (23, 28). For all study subjects, AF diagnosis was determined by linking the subjects' personal identification numbers to the Swedish Patient Register, starting from 1987 and until the end of our follow-up in 2011. AF was defined as presence of any of the following ICD codes: 427D for ICD-9 and I48 for ICD-10 (28).

The Swedish Cause of Death Register is maintained by the Swedish National Board of Health and Welfare and contains information from 1961 until present day. The information is derived from death records, including the underlying cause and up to 20 contributory causes of death coded to the current ICD edition at time of death. ICD-10 was used for our study population (60, 61). Information was gathered starting from the date of admission with ischemic stroke or the date of enrollment in the study, and ending at the conclusion of the 10-year follow-up. AF was defined as the presence of the I48 code from the ICD-10.

The first date corresponding to the AF code was considered to be the date AF was documented in the national registers.

Clinical types of atrial fibrillation: definitions

AF clinical types at the time the patient was admitted with stroke or enrolled in LSR were determined as permanent AF or recurrent AF (62). AF was defined as recurrent in cases when it was considered to be paroxysmal AF or persistent AF (with consecutive cardioversion) by the attending physician or on the basis of ECG screening when spontaneous conversion to sinus rhythm was proven by the ECG with sinus rhythm at time of the patient's admission with ischemic stroke or at the time of enrollment. Patients who had an AF diagnosis in accordance with ICD codes retrieved from the Swedish Patient Register and had sinus rhythm at admission were considered as having recurrent AF. Permanent AF was diagnosed in accordance with the attending physician's judgment as documented in medical records, or when serial ECGs demonstrated arrhythmia without intervening sinus rhythm, including the ECG at enrollment (63).

Baseline clinical assessment

Baseline clinical assessment included demographics, comorbid conditions, such as cardiac failure, hypertension, ischemic heart diseases, stroke or transient ischemic attack in the past, diabetes, severity of stroke measured by the National Institutes of Health Stroke Scale (NIHSS) (64) (except Study III) and cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc scales (6). In Study I, the index ischemic stroke was not considered when CHADS₂ and CHA₂DS₂-VASc were calculated. In Studies III, IV, and V, the index ischemic stroke was included in calculating the scores.

ECG analysis

Standard clinical 12-lead ECG recordings with sinus rhythm were obtained at time of enrollment for all study subjects with ischemic stroke treated at Mayo Clinic (Study III), as well as for ischemic stroke patients from the LSR cohort (Study IV). Digital signals were extracted and stored in a format readable by the MegaCare ECG management system (Siemens-Elema, Stockholm, Sweden. Discontinued). Standard clinical measurements, i.e. P-wave duration, QRS duration, corrected QT interval (using Bazett's formula), PQ interval and P-wave terminal force in Lead V1 were obtained from the MegaCare system using the University of Glasgow 12-lead ECG analysis algorithm (65). P-wave terminal force in Lead V1 was defined as the duration in milliseconds of the terminal (negative) part of the P wave multiplied by its depth in millimeters (Figure 5) (66).



Figure 5
P terminal force in Lead V1.

P-wave morphology assessment was performed using custom-made software running on MATLAB R2013b (The MathWorks, Inc., Natick, MA, USA) for Linux. The 12-lead ECG was mathematically transformed into orthogonal leads using the pseudo-inverse of the Dower transformation matrix (67). The orthogonal leads were denoted X (right-left), Y (up-down), and Z (front-back).

QRS complexes were put in different clusters based on morphology (using cross-correlation as a measure of similarity). Only the largest cluster was used in the analysis as a way of removing ventricular ectopic beats and erroneous beat detections.

P-waves were extracted using 250 ms-wide signal windows preceding each QRS complex. Different clusters of the signal windows were created based on their morphology, where cross-correlation was used to measure similarity and Woody's method was used to compensate for differences in the PQ interval. The largest cluster was averaged and the actual P-wave was defined by manual setting of the onset and end of P wave (68-70).

In addition to conventional P-wave indices, gross morphology of P-waves was analyzed using an automatic algorithm (38). Orthogonal P-waves were classified into types, such as advanced interatrial block with retrograde left atrial activation (IAB) and other types. IAB was defined when P-waves with positive polarity in lead X (+) and biphasic (+/-) polarity in lead Y were registered.

Echocardiography

Results of clinically-indicated TTE were retrieved from patient medical records (Study III). TTE examinations were performed at median 1 day (IQR -10.9 to 2.9 months) from the stroke. We assessed the LAVI, ml/m², ejection fraction (EF), estimated right atrial pressure using inferior vena cava size and respiratory variation (mm Hg), right ventricular pressure (mm Hg), left ventricular end-systolic and end-diastolic internal dimensions (mm).

Long-term outcomes

The end point in this study was all-cause mortality (Study V), which was assessed via linkage with the Swedish Cause of Death Register. Vital status, dates of death, and primary and secondary diagnoses at the date of death for all stroke patients were determined from the date of stroke until the date of death or the end of follow-up. The information is derived from death records, including underlying causes of death and up to 20 contributory causes of death coded to the ICD, 10th edition (60, 61).

Oral anticoagulant therapy

Since novel oral anticoagulants were not available at the time of enrollment in the LSR, OAC therapy was limited to the use of warfarin in our study.

OAC therapy at any time prior to stroke and during 10-year follow-up (Study I, V) was assessed using the Lund University Hospital anticoagulation database that contains data for all local catchment area patients receiving OAC, including dates of starting and ending warfarin therapy, indication for OAC treatment, and International normalized ratio (INR) data. In the present study, we assessed the beginning of OAC therapy, the duration of treatment, the therapy end date, and the reasons of withdrawal for patients who were prescribed OAC.

Statistics

Normally distributed data are presented as mean values \pm standard deviations (std). Median and IQR are used in cases of asymmetrical distribution. Clinical factors, ECG and ECHO characteristics were compared across groups 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.

In order to identify the clinical factors associated with first-ever ischemic stroke (Study I) and the clinical factors, ECG and ECHO characteristics associated with AF (Study I, III), relevant and significantly associated covariates were evaluated in univariate logistic regression models with estimation of odds ratios (OR) and likelihood-ratio tests. Significantly associated factors in univariate models were included in a stepwise regression analysis with backwards elimination for assessing independent risk factors.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for register-based AF diagnosis against ECG data, considered to be the "gold standard" for verifying AF (Study II).

Receiver operator characteristics (ROC) curve analysis was used to identify the optimal cut-off of LAVI for predicting AF on ambulatory ECG monitoring with

calculation of NPV, sensitivity and specificity (Study III) and the optimal cut-off of CHADS₂ and CHA₂DS₂-VASc scales for predicting new-onset AF after ischemic stroke (Study IV).

Cox proportional hazard regression models were used to estimate the adjusted hazard ratios (HR) and their 95% confidence intervals (CI) of new onset AF associated with clinical and ECG covariates (Study IV) and mortality associated with clinical factors, AF types and OAC therapy (Study V). Univariate Cox regression analyses were performed separately for each component of the CHA₂DS₂-VASc score (Study IV, V), each ECG parameter (Study IV) and for AF types and usage of OAC (Study V). Significantly associated factors in the univariate analyses were included in a stepwise regression analysis with backward elimination.

The Kaplan-Meier product-limit method was used to generate a survival curve indicating new onset AF during 10-year follow-up after enrollment in the LSR (Study IV) and indicating survival during the 10-year follow-up after the first-ever ischemic stroke (Study V).

P-values were calculated using Fisher's exact test, with a two-tailed p-value < 0.05 being considered statistically significant.

All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Planned analyses

Study 1. Prevalence of AF and its clinical types prior to first-ever ischemic stroke

The study sample was comprised of 336 consecutive stroke patients (mean age 74±12 years, 200 men) enrolled in the LSR from March 2001 to February 2002, and 336 age- and gender-matched controls without history of stroke. AF prior to admission and its clinical types were studied using the regional electronic ECG database and record linkage with the Swedish National Patient Register. Medical records were reviewed for AF documentation and cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc risk scales. Information regarding OAC therapy prior to and at stroke onset was obtained from the Lund University Hospital anticoagulation database.

Study 2. Validation of AF diagnosis in national registers

The PPV, NPV, sensitivity and specificity of AF diagnosis were assessed against ECG documentation in 672 subjects from the LSR (336 patients with first-ever ischemic stroke and 336 control subjects). Data were exported from the Swedish National Patient Register and the Cause of Death Register in October 2011 (end of follow-up).

The first date corresponding to the AF code was considered to be the date of first AF documentation in the national registers. AF documentation by ECG was estimated using an electronic ECG archive. The first date of ECG with AF was considered to be the date of first ECG documentation of AF.

Study 3. ECG and ECHO predictors of paroxysmal AF detected after ischemic stroke

Ischemic stroke patients treated at Mayo Clinic (Rochester, MN, USA) comprised the study sample as described above. The standard 12-lead ECG with sinus rhythm at stroke onset was digitally processed and analyzed to assess ECG parameters associated with AF detected during 3-week ambulatory ECG monitoring. ECHO characteristics were analyzed using TTEs data retrieved from medical records of all study subjects.

Study 4. Predictors of new-onset AF during the 10 years following the first-ever ischemic stroke

After excluding first-ever ischemic stroke patients with documented AF (n=109) (Study I), the study sample was comprised of 227 patients (mean age 71 ± 12 years, 92 female) and 227 age- and gender-matched controls without AF selected from the main study cohort. New-onset AF during follow-up was assessed by screening through regional ECG database and by record linkage with the Swedish National Registers. The standard 12-lead sinus rhythm ECGs taken at time of hospital admission with stroke were retrieved from the electronic database and digitally processed in order to assess ECG parameters associated with new-onset AF during the 10-year follow-up after the first-ever ischemic stroke. Clinical predictors of new-onset AF were studied using medical records.

Study 5. Impact of AF, its clinical types and secondary prevention therapy on long-term prognosis in patients with ischemic stroke

In this study, only first-ever ischemic stroke patients from the LSR were included (n=336). All patients were followed up for 10 years. At baseline, 109 patients had either permanent AF (n=44) or recurrent AF (n=65) (Study I). OAC was analyzed through the Lund University Hospital anticoagulation database. The endpoint in this study was all-cause mortality assessed via linkage with the Swedish Cause of Death Register.

Results

Baseline assessment of patients in the Lund Stroke Register cohort

Baseline characteristics of study groups are summarized in Table 1. The cardiovascular risk profile (CHA₂DS₂-VASc score) was higher in the stroke group than in the control group: patients with ischemic stroke had greater incidence of history of cardiac failure, hypertension, diabetes mellitus, ischemic heart disease and transient ischemic attack.

Ischemic stroke was independently associated with AF (OR 2.55 95%CI 1.67-3.89, p<0.001), diabetes mellitus (OR 1.98 95%CI 1.13-3.45, p=0.016), previous transient ischemic attack (OR 4.29 95%CI 2.56-7.21, p<0.001), hypertension (OR 1.89 95%CI 1.33-2.68, p<0.001) and vascular disease (OR 2.27 95%CI 1.54-3.33, p<0.001).

Table 1

Baseline clinical characteristics of stroke patients and control subjects enrolled in the LSR.

Variables	Stroke group			Control group		
	All, n=336	AF, n=109	No AF, n=227	All, n=336	AF, n=44	No AF, n=292
Women, n (%)	136(41)	44(40)	92(41)	136(41)	22(50)	114(39)
Age, mean±std	74±12	80±8	71±12**	74±12	82±7	73±12***
Cardiac failure, n (%)	8(8)	21(19)	7(3) **	14(4) *	7(16)	7(2) ***
Hypertension, n (%)	195(58)	65(60)	130(57)	114(34) *	21(48)	93(32) ***
Diabetes, n (%)	63(19)	28(26)	35(15) **	23(7) *	5(11)	18(6)
TIA, n (%)	74(22)	25(23)	49(22)	4(1) *	2(5) ****	2(1)
Vascular diseases, n (%)	142(42)	47(43)	95(42)	62(19) *	18(41)	44(15) ***
CHA ₂ DS ₂ -VASc, mean±std	3.5±1.7	4.0±1.6	3.2±1.7**	2.4±1.5*	3.6±1.2	2.2±1.4***
NIHSS score, mean±std	6.5±7.5	8.9±9.3	5.3±6.2**	-	-	-
AF at baseline, n (%)	109(32)		-	44(13) *		-
Permanent AF, n (%)	44(13)	44(40)	-	9(3)	9(20) ****	-
Recurrent AF, n (%)	65(19)	65(60)	-	35(10)	35(80)	-

* - p<0.05 in comparison with stroke group

** - p<0.05 in comparison with AF patients in stroke group

*** - p<0.05 in comparison with AF patients in control group

**** - p<0.05 in comparison with AF patients in stroke group

Evidence of atrial fibrillation prior to ischemic stroke

70 stroke patients (20.8%) had AF on admission ECG; 24 of these patients (7.1%) had no prior documentation or history of AF. For 22 stroke patients (6.5%) who presented with sinus rhythm at baseline, AF was found on at least one of their historical ECGs. Of these 22 patients, 14 patients (4.2%) had no history of prior AF in their admission medical records. Six stroke patients (1.8%) had AF history documented in medical records, although ECG did not show AF prior to or at inclusion (Figure 6).

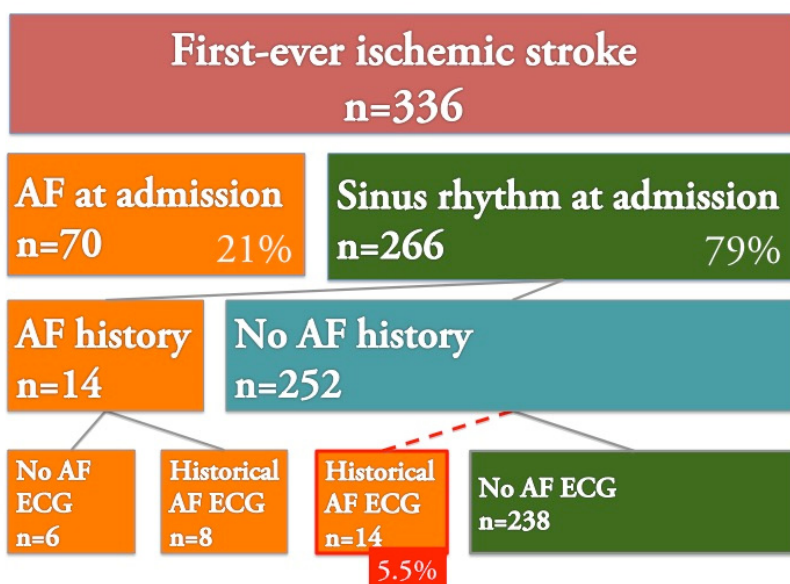


Figure 6

ECG detection of AF in first-ever ischemic stroke patients in the Lund Stroke Register. Additional 5.5% of new AF cases were found by retrospective ECG screening in stroke patients with sinus rhythm on ECG taken at admission and with no AF history in their medical records.

In the control group, AF at any time prior to enrollment was found on ECGs for 30 subjects (8.9%), and 2 subjects (0.6%) had AF history documented in medical records.

Record linkage with the Swedish Patient Register revealed 11 additional ischemic stroke patients (3.3%) and 12 controls (3.6%) with AF diagnosis for whom no AF ECG was found in the ECG databases, nor was there information about AF in their medical records.

In total, AF by baseline was diagnosed in 109 patients (32.4%) and in 44 control subjects (13.1%) ($p < 0.001$, Figure 7).

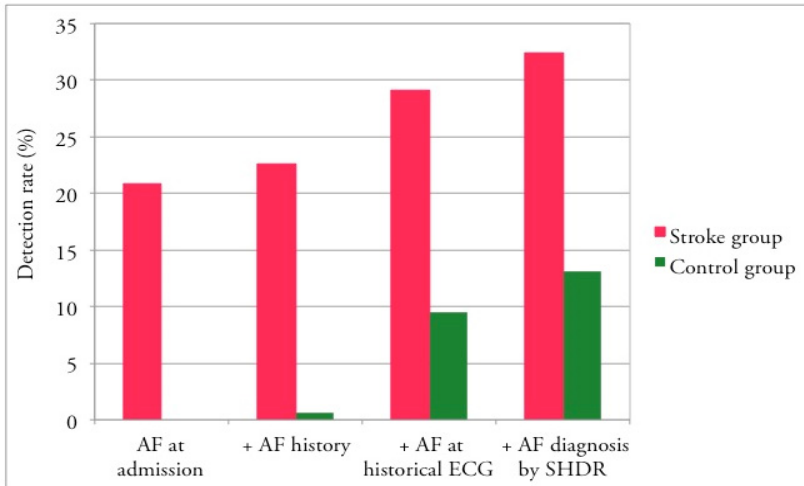


Figure 7
Cumulative detection rate of AF (%) documented by admission ECG, reviewing medical records for AF history, retrospective ECG screening and record linkage with the Swedish National Patient Register.

ECG validation of register-based diagnosis of atrial fibrillation

A total of 7,247 ECG recordings were available and were reviewed for our study population. The median number of available ECGs per person was 7.5 (IQR 3-15) and was significantly higher for patients and controls with documented AF than for patients and controls without documented AF: 13 (IQR 8-23) vs 6 (IQR 3-11), $p < 0.001$. The earliest AF documented by ECG was dated March 14, 1989, and the first AF diagnosis in the Swedish Patient Register was dated January 12, 1987.

AF by ECG could be detected in 190 study subjects, while 185 subjects had AF diagnosis in the Swedish National Patient Register, and 3 had AF diagnosis in the Swedish Cause of Death Register only, thus bringing the total number of AF cases obtained from national registers to 188 (Figure 8). Due to the low number of AF cases obtained from the Swedish Cause of Death Register and for the sake of brevity, the combined source of diagnostics information from the two national registries was denoted as register-based diagnosis.

		AF by ECG		
		AF	No AF	
AF by SNPR	AF	152	36	PPV 81%
	No AF	38	446	NPV 92%
		Sensitivity 80%	Specificity 93%	

Figure 8
PPV, NPV, sensitivity and specificity of register-based AF diagnosis in the Swedish National Patient Register (SNPR) against ECG documentation.

AF diagnosis by both ECG and national registers coincided in 152 subjects. In most cases (86%), AF was first documented by ECG. The median time from the date of first AF on ECG to the date of register-based diagnosis was 16 days (IQR 3-859). In 51 subjects (34%) with ECG-verified AF diagnosis, the time lapse between the dates of ECG documentation and diagnosis in the register was greater than 6 months. For 446 individuals, AF was neither detected by ECG nor recorded in the national registers. Despite the high specificity of register-based AF diagnosis, its sensitivity did not exceed 80%. PPV, specificity and sensitivity did not differ between stroke group and control group, although NPV was lower in stroke patients (Figure 9, Table 2).

Stroke group

Control group

		AF by ECG		
		AF	No AF	
AF by SNPR	AF	104	19	PPV 85%
	No AF	23	190	NPV 89%
		Sensitivity 82%	Specificity 91%	

		AF by ECG		
		AF	No AF	
AF by SNPR	AF	48	17	PPV 74%
	No AF	15	256	NPV 94%
		Sensitivity 76%	Specificity 94%	

Figure 9
PPV, NPV, sensitivity and specificity of register-based AF diagnosis in the Swedish National Patient Register (SNPR) against ECG documentation in stroke group and in the control group.

Table 2

Comparison of PPV, NPV, sensitivity and specificity of atrial fibrillation diagnosis in the Swedish National Patient Register in stroke patients vs. control subjects.

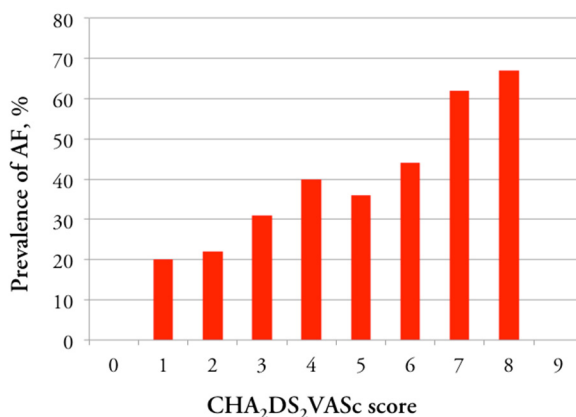
	All patients, n=672	Stroke group, n=336	Control group, n=336	P-value
PPV, %	81	85	74	0.076
NPV, %	92	89	95	0.033
Sensitivity, %	80	82	76	0.355
Specificity, %	93	91	94	0.236

Clinical characteristics associated with atrial fibrillation in ischemic stroke patients

Prevalent atrial fibrillation

In patients with first-ever ischemic stroke from the LSR (Study I), AF prior to stroke was independently associated with age (OR 6.61 95%CI 2.60-16.81, $p < 0.001$) and cardiac failure (OR 1.08 95%CI 1.05-1.11, $p < 0.001$).

The pre-stroke prevalence of AF was higher in patients with a higher cardiovascular risk profile measured by CHA₂DS₂-VASc scale (Figure 10).

**Figure 10**

The distribution of AF in stroke patients according to CHA₂DS₂-VASc score.

In the Mayo Clinic ischemic stroke cohort (Study III), patients with history of paroxysmal AF had a higher proportion of vascular diseases, cardiac failure and higher cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc scales than patients without AF at baseline (Table 3). However, in the multivariate logistic

regression analysis only vascular diseases (OR 4.10 95%CI 1.32-12.78, p=0.015) remained significantly associated with AF prior to stroke.

Table 3

Baseline clinical characteristics in ischemic stroke patients without AF at stroke onset in comparison with ischemic stroke patients with history of paroxysmal AF prior to stroke.

Variables	Patients without AF, n=110	Patients with AF history, n=55	P value
Mean age, years \pm std	67 \pm 10	68 \pm 10	0.686
Female, n (%)	40 (36)	19 (35)	0.864
Diabetes, n (%)	18 (16)	12 (22)	0.399
Hypertension, n (%)	84 (76)	41 (75)	0.848
Vascular diseases, n (%)	21 (19)	20 (36)	0.021
Cardiac failure, n (%)	6 (6)	16 (29)	<0.001
CHADS₂ score, mean \pm std	3.2 \pm 0.9	3.5 \pm 1.0	0.034
CHA₂DS₂-VASc score, mean \pm std	4.9 \pm 1.5	4.9 \pm 1.5	0.028

Incident atrial fibrillation

In the stroke cohort from Mayo Clinic, incidence of AF was assessed early after stroke onset. Among patients without AF at baseline who underwent 3-week ambulatory ECG monitoring at median 24 days (IQR 7-47) after stroke onset (Study III), short AF episodes of median 6 seconds duration (IQR 6-9) were detected in 24 patients (22%). Patients with AF detected on ECG monitoring were older (mean age 71 \pm 9 years vs 66 \pm 10 years, p=0.033) than patients without detected AF, with no differences in sex, cardiovascular comorbidities and cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc scales (Table 4). In a univariate regression analysis, detection of short AF episodes after stroke was associated with age (OR 1.05 95%CI 1.00-1.11, p=0.037). However, after adjustment for the left atrial size measured as LAVI, age did not remain significantly associated with short AF episodes during ambulatory ECG monitoring.

Table 4

Baseline clinical characteristics in ischemic stroke patients without AF in comparison with ischemic stroke patients with detected paroxysmal AF using ambulatory ECG monitoring.

Variables	Patients without any AF, n=86	Patients with detected AF, n=24	P value
Mean age, years \pm std	66 \pm 10	71 \pm 9	0.033
Female, n (%)	55 (64)	15 (63)	1.000
Diabetes, n (%)	17 (20)	1 (4)	0.115
Hypertension, n (%)	66 (76)	18 (75)	1.000
Vascular diseases, n (%)	17 (20)	4 (17)	1.000
Cardiac failure, n (%)	4 (5)	2 (9)	0.604
CHADS ₂ score, mean \pm std	3.2 \pm 0.9	3.2 \pm 0.9	0.996
CHA ₂ DS ₂ -VASc score, mean \pm std	4.3 \pm 1.5	4.5 \pm 1.4	0.579

Incidence of AF during long-term follow-up (median time 9.4 years [IQR 6.1-9.9]) was assessed in the LSR cohort of patients with first-ever ischemic stroke. New onset

AF was found in 69 (15%) study subjects from the LSR cohort (Study IV): 39 (17%) stroke patients and 30 (13%) control subjects (HR 1.46 95% CI 0.90-2.35, $p=0.121$), (Figure 11).

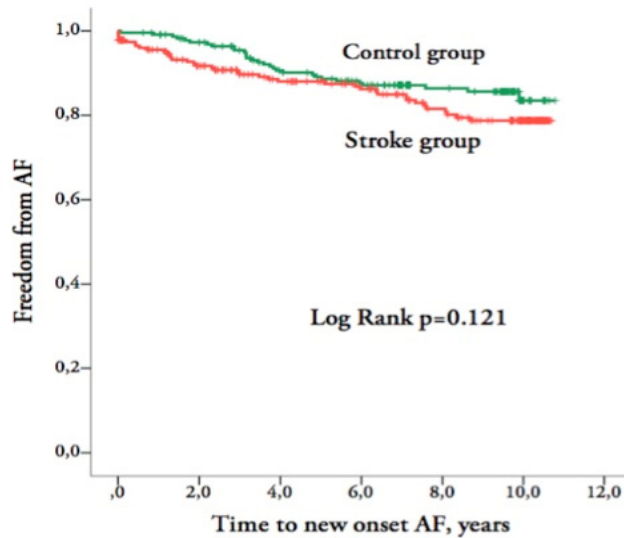


Figure 11

Kaplan-Meier survival curve indicating new-onset AF during 10-year follow-up in ischemic stroke patients and control subjects.

In the univariate Cox regression analysis for stroke patients, the incidence of AF during 10-year follow-up was associated with hypertension (HR 2.37 95% CI 1.15-4.86, $p=0.019$), cardiac failure (HR 4.04 95% CI 1.24-13.18, $p=0.020$) and age >65 years (HR 2.88 95% CI 2.20-6.89, $p=0.018$). In the multivariate Cox regression analysis, only hypertension remained an independent predictor of new onset AF (HR 3.45 95% CI 1.40-8.49, $p=0.007$).

The areas under the ROC curve values for the CHADS₂ and CHA₂DS₂-VASc scales for predicting AF occurrence were 0.615 ($p=0.024$) and 0.606 ($p=0.037$), respectively. The optimal cutoff 3.5 for the CHADS₂ scale had sensitivity of 49%, specificity of 68% and negative predictive value of 86%. Cutoff 4.5 for the CHA₂DS₂-VASc scale had sensitivity of 77%, specificity of 44% and negative predictive value of 90%. High cardiovascular risk was predictive for AF development in the multivariate Cox regression analysis: for CHADS₂ ≥ 4 HR 2.46 CI 95% 1.45-4.18, $p=0.001$ and for CHA₂DS₂-VASc ≥ 5 HR 2.29 CI 95% 1.43-3.68, $p=0.001$ (Figure 12).

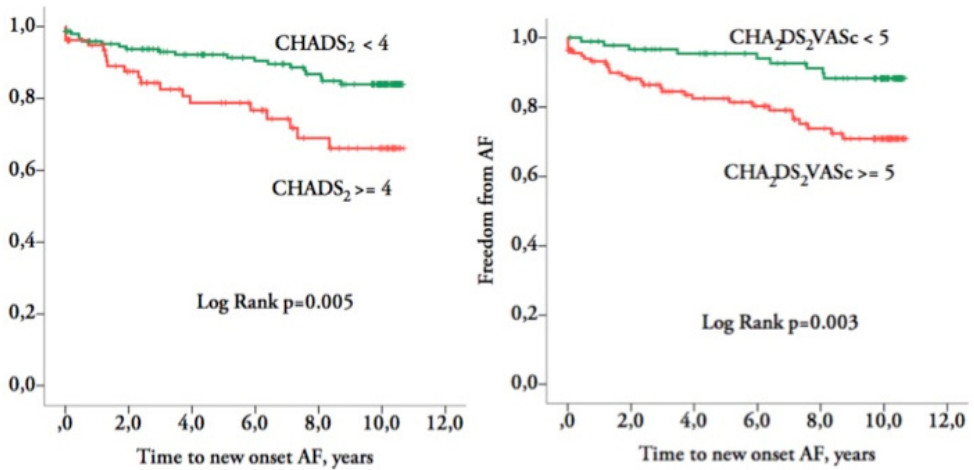


Figure 12 Kaplan-Meier survival curve indicating new-onset AF during 10-year follow-up in ischemic stroke patients according to different CHA₂DS and CHA₂DS₂VASc scores in stroke patients without AF at their baseline stroke.

ECG characteristics associated with atrial fibrillation

Among patients with first-ever ischemic stroke from the LSR, 182 patients without AF at baseline and 52 patients with history of paroxysmal AF had available ECG on sinus rhythm at admission. Patients with AF had longer PR intervals than patients without AF and did not differ in other ECG characteristics (Table 5). After adjustment for age and cardiac failure, PR interval remained independently associated with history of paroxysmal AF (OR 1.01 95%CI 1.00-1.03, p=0.010).

Table 5

ECG characteristics in ischemic stroke patients without AF at stroke onset in comparison with ischemic stroke patients with history of paroxysmal AF prior to stroke.

Variables	Lund Stroke Register cohort			Mayo Clinic cohort		
	No AF, n=182	Patients with paroxysmal AF, n=52	P value	Patients without AF, n=110	Patients with AF history, n=55	P value
P-wave duration, ms, mean±std	115 ± 17	116 ± 17	0.661	113 ± 18	120 ± 17	0.021
PR - interval, ms, mean±std	168 ± 29	189 ± 38	0.001	172 ± 28	178 ± 35	0.189
P-wave terminal force in lead V ₁ , mm x ms, mean±std	22 ± 20	21 ± 21	0.816	24 ± 26	35 ± 33	0.020
QRS duration, ms, mean±std	99 ± 21	102 ± 20	0.325	100 ± 17	107 ± 21	0.021
Corrected QTc interval, ms, mean±std	437 ± 31	444 ± 33	0.173	430 ± 28	454 ± 34	<0.001
IAB, n (%)	6 (3)	3 (5)	0.693	5 (5)	6 (11)	0.183

In the *post hoc* analysis from the Mayo Clinic prospective study (Study III), analysis of ECG data showed that P-wave duration, QRS duration and corrected QT interval were longer, and P-wave terminal force in lead V₁ was greater in stroke patients with AF history than in patients without AF at stroke. The prevalence of IAB was similar in both groups (Table 5).

In the multivariate logistic regression analysis, only P-wave terminal force in lead V₁ greater than 40 mm*ms (OR 4.04 95%CI 1.34-12.14, p=0.013) remained independently associated with AF prior to stroke.

Patients with incident AF early after stroke and patients without any AF from the Mayo Clinic cohort (Study III) did not differ in any ECG parameters, including P-wave morphology, except the differences in the PR-interval, which was longer in stroke patients without AF in comparison with stroke patients with detected AF (Table 6). However, in the multivariate regression analysis after adjustment for age PR interval was not associated with AF detected during ambulatory ECG monitoring (OR 0.97 95%CI 0.94-1.00, p=0.071).

Table 6

ECG characteristics in ischemic stroke patients without AF at stroke onset in comparison with ischemic stroke patients with incident AF detected by 3-week ambulatory ECG monitoring (Mayo Clinic cohort)

Variables	Patients without any AF, n=86	Patients with detected AF, n=24	P value
P-wave duration, ms, mean±std	136 ± 15	143 ± 18	0.232
PR - interval, ms, mean±std	175 ± 29	158± 22	0.007
P-wave terminal force in lead V1, mm x ms, mean±std	23 ± 24	28 ± 35	0.394
QRS duration, ms, mean±std	100 ± 18	100 ± 15	0.962
Corrected QTc interval, ms, mean±std	430 ± 28	430 ± 28	1.000
IAB, n (%)	5 (6)	0 (0)	0.584

In the long-term follow up of the stroke cohort (Study IV), only QRS duration was predictive of new onset AF during 10 years after first-ever ischemic stroke (Table 7) in univariate Cox regression analysis. After adjustment for significantly associated clinical factors (age, hypertension and cardiac failure), QRS duration remained an independent (although borderline significant) predictor of new-onset AF during 10 years after first-ever ischemic stroke (HR 1.02 95% CI 1.00-1.03, p=0.049).

Table 7

ECG predictors of new onset AF during 10-year follow-up in ischemic stroke patients without known AF at their index stroke.

Variable	Univariate Cox regression analysis		
	HR	95% CI	P value
QTc interval	1.01	1.00-1.02	0.104
P wave duration	1.02	0.96-1.05	0.105
QRS duration	1.02	1.00-1.04	0.025
PQ interval	1.00	0.99-1.01	0.966
P terminal force amplitude in lead V1	1.00	1.00-1.00	0.142

Echocardiographic parameters associated with atrial fibrillation

Among all parameters assessed by TTE (Study III), only LAVI was significantly and independently associated with history of paroxysmal AF (OR 1.08 95%CI 1.03-1.13, $p=0.002$) and with AF detected on ambulatory ECG monitoring (OR 1.08 95%CI 1.01-1.15, $p=0.017$).

In stroke patients with history of paroxysmal AF, LAVI was 45 ± 12 ml/m², in stroke patients with detected short episodes of AF LAVI was 42 ± 15 ml/m², and in stroke patients without any AF LAVI was 32 ± 10 ml/m².

The area under the ROC curve values for LAVI as an indicator of short AF episodes detected by ambulatory ECG monitoring was 0.698, $p=0.041$ (Figure 13). A cutoff of <40 mL/m² had an 84% negative predictive value for ruling out AF on ambulatory monitoring with sensitivity of 50% and specificity of 86%.

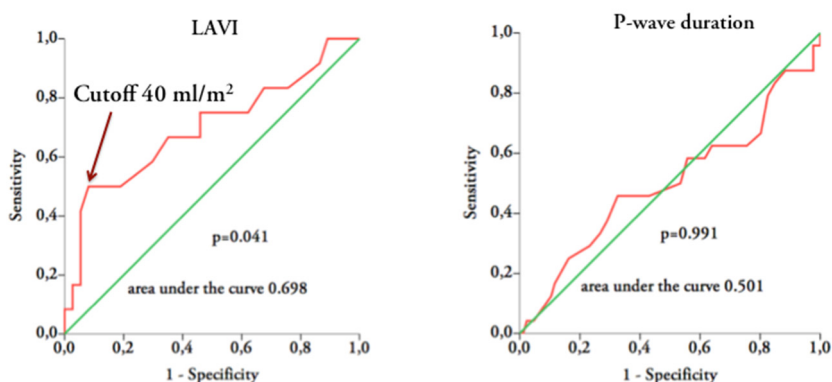


Figure 13

ROC curves for diagnostic values of LAVI and P-wave duration for detecting short episodes of AF on ambulatory ECG monitoring. While increased LAVI (left panel) has demonstrated significant predictive value for AF detection (optimal cut-off 40 ml/m², specificity 86%, sensitivity 50%, NPV 84%), none was demonstrated for conventional ECG-based markers such as P-wave duration (right panel) or P-wave terminal force in lead V1 (not shown).

Clinical types of atrial fibrillation: prevalence at stroke onset and impact on long-term prognosis

The most common type of AF at stroke onset in the LSR cohort (Study I) was recurrent AF (60%). Patients with permanent AF were older than patients with recurrent AF (mean age 83 ± 7 years vs 78 ± 9 years, $p=0.003$) and did not differ in either cardiovascular risk factors or stroke severity (Table 8).

Table 8

Baseline clinical characteristics in first-ever ischemic stroke patients without AF, with permanent AF and with recurrent AF.

Variable	No AF, n=227	Permanent AF, n=44	Recurrent AF, n=65	P value for permanent AF vs recurrent AF
Age, mean±std	71±12	83±7	78±9	0.003
Females, n (%)	92 (41)	18 (41)	26 (40)	1.000
Cardiac failure, n (%)	7 (3)	9 (21)	12 (19)	0.809
Hypertension, n (%)	130 (57)	28 (64)	37 (57)	0.533
Diabetes, n (%)	35 (15)	12 (27)	16 (25)	0.825
Vascular diseases, n (%)	95 (42)	16 (36)	31 (48)	0.324
CHA ₂ D ₂ S-VASc, mean±std	3.2±1.7	4.3±1.7	3.8±1.6	0.130
NIHSS scale, mean±std	5.3±6.2	8.8±9.0	9.0±9.6	0.885

322 (96%) patients were discharged alive (Study V). Among 14 patients who died before discharge from the hospital, 11 patients had AF: permanent AF in 4 patients and recurrent AF in 7 patients (p=1.000). In multivariate logistic regression analysis after adjustment for age and clinical factors, only severity of stroke measured by the 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.

In total, during the 10-year 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 the 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). The highest impact on mortality was found for permanent AF (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 (Figure 14).

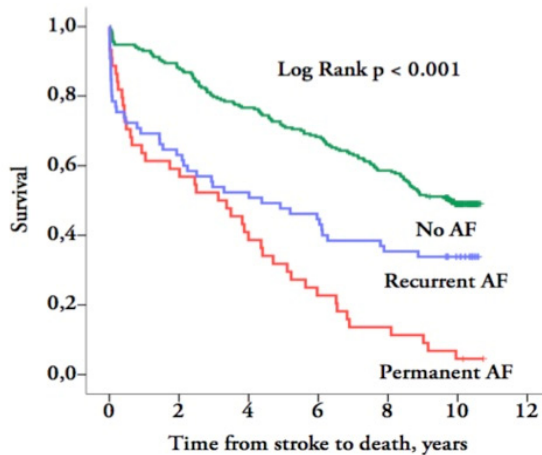


Figure 14
Kaplan-Meier survival curve indicating survival during 10-year follow-up in stroke patients without AF, with permanent AF and with recurrent AF.

Oral anticoagulant therapy at stroke admission and during 10-year follow-up

OAC therapy at any time prior to first-ever ischemic stroke (Study I) among patients with AF and indications for secondary prevention therapy (54 patients in the stroke group) was administered in 20% of cases. 14 patients, of which 10 had known AF, had their first-ever ischemic stroke onset while being treated with OAC. Of the 10 patients, 8 AF patients had CHADS₂ ≥ 2. Only 3 of the 8 patients had INR ≥ 2 at the time of stroke. Three patients had INR <2, and for 2 patients, INR data during stroke admission were not available.

In the LSR cohort (Study V), 98 (90%) stroke patients with AF were discharged alive (40 with permanent AF and 58 with recurrent AF, $p=1.000$); 38 of the 98 patients (39%) were prescribed vitamin K antagonist warfarin: 18 of the 40 patients with permanent AF (45%) and 20 of the 58 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). In total, 44 stroke patients with AF (45%) received secondary prevention therapy during follow-up, with median time on OAC being 4.8 years (IQ 0.9-8.8 years) for patients with permanent AF and 8.6 years (IQ 2.7-9.1 years) for patients with recurrent AF, $p=0.158$. 26 patients (59%) continued receiving OAC until the end of follow-up ($n=18$) or death ($n=8$); 6 patients ended OAC therapy

due to complications; 5 ended OAC therapy due to difficulties with warfarin dosage, 8 patients ended OAC therapy for patients own choice.

At discharge, 4 patients with recurrent AF were not prescribed any antithrombotic medication. 22 patients with permanent AF (55%) and 34 patients with recurrent AF (59%) received antiplatelet medications (either aspirin or clopidogrel); only one patient received combined therapy: aspirin plus clopidogrel. During follow-up, the worst prognosis was observed for the 4 patients without antithrombotic therapy, the 46 patients receiving antiplatelet therapy had better prognosis compared to patients without antithrombotic therapy (HR 0.28 95% CI 0.13-0.58, $p=0.001$), and the best prognosis was observed for the 44 patients receiving warfarin compared to patients without antithrombotic therapy (HR 0.10 95% CI 0.05-0.23, $p<0.001$), Figure 15.

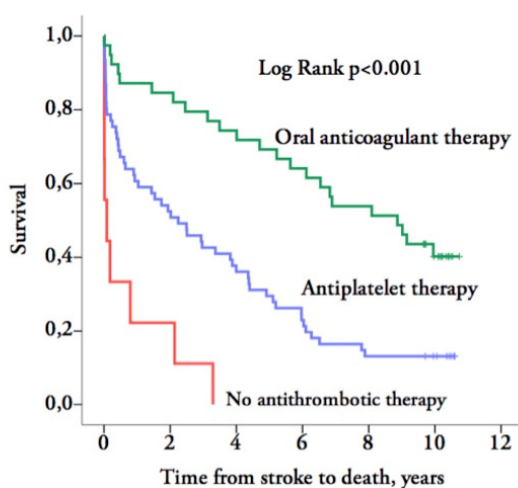


Figure 15

Kaplan-Meier survival curve indicating survival during 10-year follow-up according to discharge therapy in stroke patients with atrial fibrillation.

During the 10-year follow-up, patients with recurrent AF treated with OAC had similar survival rates to patients without AF history (HR 0.71 95%CI 0.37-1.36, $p=0.299$). Prognosis was the worst for patients with permanent AF without OAC (HR 2.27 95%CI 1.40-3.66, $p=0.001$), and was intermediate for patients with permanent AF on OAC (HR 1.61 95% CI 0.96-2.70, $p=0.071$). In AF patients discharged without OAC, the type of AF did not appear to influence the long-term outcomes (Figure 16, Table 9).

Patients with permanent AF receiving OAC had a higher risk of mortality than patients with recurrent AF receiving OAC (adjusted HR 2.72 95% CI 1.04-4.98, $p=0.04$).

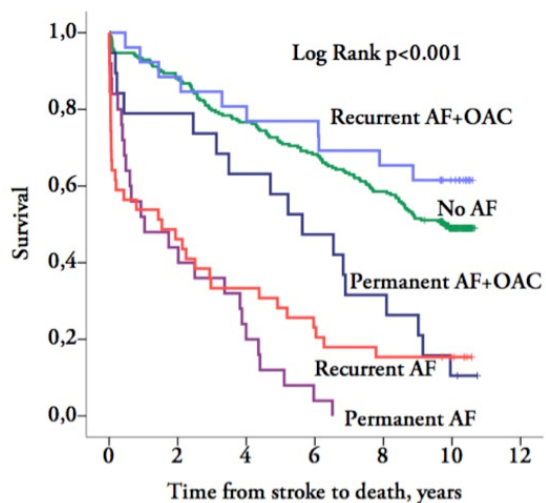


Figure 16
Kaplan-Meier survival curve indicating survival during 10-year follow-up according to different clinical types of AF and OAC therapy in stroke patients.

Table 8
Cox regression analysis in patients with different clinical types of AF receiving or not receiving OAC therapy for prediction of 10-year all-cause mortality.

*-reference group – patients without AF.

Variable	Univariate analysis			After adjustment for independent predictors of mortality		
	HR *	95% CI	P value	HR	95%CI	P value
Recurrent AF +OAC	0.71	0.37-1.34	0.300	0.71	0.37-1.36	0.299
Permanent AF +OAC	2.34	1.41-3.90	0.001	1.61	0.96-2.70	0.071
Recurrent AF -OAC	3.74	2.53-5.52	<0.001	1.80	1.20-2.71	0.005
Permanent AF -OAC	6.09	3.87-9.60	<0.001	2.27	1.40-3.66	0.001

Discussion

Evidence of atrial fibrillation prior to ischemic stroke

One of the main findings of this thesis is the high pre-stroke prevalence of AF. A cumulative detection rate of AF 32.4% before or at ischemic stroke onset was higher than in previous population-based studies in which AF was documented at index admission on the basis of clinical information or admission ECG. Those earlier studies reported AF prevalence in stroke patients as not exceeding 25% (7, 71). Routine ambulatory 24-48 hour ECG monitoring in patients with ischemic stroke and sinus rhythm at admission makes AF identification possible in 1% - 6.4% of patients with no previous history of AF (12, 14, 15).

In remarkable agreement with the above-cited reports, 20.8% of first-ever ischemic stroke patients had AF on ECG at admission. Unlike previous studies, which used dedicated ECG screening for AF, the present study was focused on evaluating information available to physicians at the time of admission with stroke. We have shown that review of historical ECGs, if available at time of admission, makes AF detection possible in the range comparable to the range reported by using conventional 24-48 hour ambulatory ECG monitoring. It would be intriguing to evaluate possible additional diagnostic value of routine Holter ECG monitoring for detecting AF that is not discovered using historical ECG screening.

The probability of AF being causatively linked to ischemic stroke is likely to be higher for AF observed prior to stroke, which is why we focused our analysis on AF history/records prior to admission/enrollment. Most previous studies that reported high prevalence of AF in the stroke population included AF episodes first detected after stroke using dedicated AF screening measures. One also cannot completely rule out the probability of electrophysiological changes in the heart appearing as a consequence of ischemic stroke thus leading to development of atrial fibrillation after the stroke has occurred.

The combined approach for AF screening through electronic ECG archives and by linkage with the Swedish National Patient Register led to AF detection in 32.4% of ischemic stroke patients. National patient registry data on AF in stroke cohort have been used previously in the RIKS-Stroke study, in which AF at baseline was assessed by a self-reported questionnaire and by linkage with the Swedish National Patient Register. Using this approach, the prevalence of AF in stroke population was reported to be high, and was in the same range as reported by us (30%) (24).

Notably, AF detection rate among age- and gender-matched controls using the same combined approach reached 13.1%, which is in agreement with the data that

reported the prevalence of AF detected by stepwise ECG screening being 14% in aging Swedish population (72).

Validity of register-based atrial fibrillation diagnosis

In epidemiological studies, the diagnosis of AF is usually based on data from national patient registers. However, ECG documentation of AF is considered to be the “gold standard” of AF verification. Data from the Swedish National Patient Register and 7,247 available ECG recordings were used in a validation study of AF diagnosis recorded in the Swedish Patient Register. Having a large unselected cohort of consecutively-enrolled patients, including subjects both with and without AF diagnosis, and access to a large number of digitally-stored ECGs enabled us to assess both sensitivity and specificity of register-based AF diagnoses.

One of the most important findings of the present study is that using register-based information to estimate the number of AF cases can result in underestimating the prevalence of AF by at least 20%, which corresponds to the number of subjects who had ECG documentation of AF but had no AF diagnosis in the Swedish National Patient Register. In one recent study (73), Swedish Patient Register appeared to underestimate AF diagnosis in ischemic stroke patients by 23% when compared with information on AF diagnosed by primary care facilities. This further highlights the importance of access to either ECG documentation or clinical information collected by primary care providers in order to assess the presence of AF in high-risk patient groups.

In the present study, PPV of register-based AF diagnosis was 81% - lower than the PPV of 97% previously reported for AF diagnosis in the Swedish National Patient Register (28). The difference in results between the two studies may be due to two reasons. On the one hand, the previous study performed AF diagnosis validation in a randomly selected sample of 100 patients with a positive AF diagnosis. On the other hand, the study population in the previous study (28) was randomly selected from a prospective epidemiological cohort with a specific standardized protocol for registering their health status, and therefore those study subjects had been more thoroughly examined and had more extensive medical documentation, including ECG recordings, than the patients enrolled in the Lund Stroke Register. It is also possible that patients included in the present study may have had ECG recordings showing AF that were not properly archived and were unavailable for review, thus leading to possible underestimation of the number of ECG-confirmed AF cases.

Only a small number of studies have addressed AF diagnosis validation in other countries. In a recent Danish study, the PPV for AF diagnosis in the Danish National Patient Registry in a selected sample of 300 patients was reported to be 92% using a combination of ECG and medical record information (74). In our study, only ECG data were used to confirm AF, which explains why validity of AF diagnosis in the Swedish Patient Register (i.e. PPV) appeared to be lower than previously reported in

studies based on combined information sources (28, 74, 75). However, in the Danish study (74), AF diagnosis was definitively confirmed by relevant documentation in only 229 of 284 patients (81%), which is in line with our findings.

The sensitivity, specificity and PPV were similar for stroke patients and control subjects, and were comparable with the data reported for the entire study population, which supports the reliability of these estimates. The only difference was found for NPV, which was lower in the stroke population (89%) than in the control population, likely due to higher prevalence of AF in stroke patients than in control subjects.

Despite the high NPV related to the relatively low prevalence of AF in the studied population, the sensitivity of AF diagnosis in the Swedish Patient Register appears to be rather modest, and indicates that the actual number of stroke patients with AF may be at least 20% higher than the number of patients assessed using only the Swedish Patient Register. The underestimation of AF in the Swedish Patient Register can be explained in part by the fact that AF may have been considered as a comorbidity not necessarily present or requiring intervention at the time of hospital admission, and for that reason not indicated as a diagnosis.

ECGs uploaded to the regional archive reflect predominantly symptomatic AF that leads patients to seek medical attention, yet true prevalence of AF in the overall population is likely underestimated. However, as recent studies show (10, 72, 76), dedicated AF screening makes it possible to detect additional cases of asymptomatic or mildly symptomatic AF.

In most patients, ECG diagnosis of AF preceded AF registration in the Swedish Patient Register – most likely because AF was first documented at the primary care level and not in the hospital. While electronic ECG archives cover both primary care facilities and in-hospital units, the Swedish Patient Register only contains information on patients who were hospitalized, thus explaining the time lapse of over 6 months for approximately one-third of all cases (6 months elapsed between the date of the first ECG recording with AF to the date corresponding to AF code being entered in the Swedish Patient Register).

The time lapse in AF diagnosis may cause a situation where the Swedish Patient Register does not provide complete information about AF prevalence at a certain point in time, thus decreasing register data reliability. Nevertheless, the median time between ECG and Swedish Patient Register diagnosis was usually three weeks or less, which indicates that such a time lapse should not significantly affect register data validity. Additional information from outpatient care providers may further improve the validity of register-based identification of patients with AF.

Atrial fibrillation detected using ambulatory ECG monitoring after ischemic stroke

In patients without AF history at stroke onset, very short episodes of paroxysmal AF were found during 3 weeks of ECG monitoring. It is still under discussion whether ultra-short AF episodes (lasting less than 30 seconds) have the same risk of thromboembolic complications as manifested AF (77). However, it has been shown that supraventricular runs and high supraventricular ectopic activity are predictive of AF occurrence (78, 79). In ischemic stroke patients, premature atrial complexes that occur more frequently than 4 per hour and atrial runs that exceed 5 complexes were associated with the occurrence of paroxysmal AF (80). Studies with loop recorders implanted for AF screening after ischemic stroke reported the AF of 2 minutes or more in duration being detected on average 48-68 days after implantation (81, 82). It is likely that, while short episodes of paroxysmal AF were common for the ischemic stroke patients who underwent ambulatory ECG monitoring for 3 weeks, the monitoring time was not long enough to reveal the full incidence of underlying asymptomatic AF in this stroke cohort. Short episodes of paroxysmal AF may be considered to be precursors of prolonged AF, and these short episodes should be used to identify stroke patients who would benefit from continuous AF screening.

Whether short episodes of AF indicate the need for anticoagulation therapy remains uncertain. The TRENDS study of patients with implantable devices showed that AF burden exceeding 5.5 hours during any preceding 30 days appeared to double the thromboembolic risk (83). However, the ASSERT study of patients with implantable devices showed that majority of patients who had stroke while being monitored do not have AF at the time of stroke onset or during the 30 days preceding stroke onset (84).

As reported recently, early anticoagulation therapy for incident AF and withdrawal after arrhythmia-free periods did not improve outcomes for patients with implantable devices as compared to conventional management of patients with AF (85). Additional studies are needed to investigate the benefit of anticoagulant therapy for patients with short asymptomatic episodes of paroxysmal AF.

New onset atrial fibrillation during 10-year follow-up after first-ever ischemic stroke

By the end of the 10-year follow-up, AF was detected in 17% of stroke patients and 13% of control subjects who did not have AF at time of stroke or time of inclusion in the LSR study. This finding corresponds to the reported AF incidence for an aging population. In one study, 18% of new AF cases were detected in people older than 85

years by the end of a 7-year follow-up (30), and another study reported AF of 17% in patients aged 65-74 years by the end of a 6-year follow-up (33).

AF screening studies performed with the use of implantable devices have generally reported much higher AF detection rates than studies based on ECG screening or national registries. The incidence of new AF during one-year follow-up was shown to be 28% in patients after ischemic stroke or TIA (86) and 30% in patients with risk factors for ischemic stroke (87). Continuous ECG recording for patients with implantable cardiac rhythm devices allowed detection of all AF episodes, including asymptomatic AF. AF detected in the present study is likely to be restricted mostly to symptomatic AF episodes, which is supported by the higher frequency of ECGs recorded in patients who eventually developed AF. More frequent ECG registration for patients with detected AF than for patients without AF may also be due to the fact that patients with detected AF had more frequent contact with health care providers due to having higher prevalence of underlying cardiovascular disorders with manifested disease symptoms. A number of asymptomatic AF episodes is likely to have been missed and thus not available for analysis.

Although literature data on this point are limited, the RIKS-Stroke study reported a higher incidence of first-ever AF in post-stroke patients than the incidence of first-ever AF calculated for the general population (23). In that study, freedom from AF at baseline was assessed by a self-reported questionnaire and by linkage with the Swedish Patient Register, and AF prevalence at baseline was reported to be high (30%) (24). However, some episodes of non-permanent AF prior to stroke may have been missed, and thus the first-ever recorded post-stroke AF may not have been the “true” first-ever AF. We reported an even higher pre-stroke AF prevalence (32%) by using ECG screening through electronic ECGs archive and record linkage with national registers (88), which likely detected AF in patients who would otherwise be considered AF-free at inclusion in the LSR, thus revealing a larger proportion of “true” new-onset AF after stroke. Our study with a 1:1 case-control design using the same comprehensive ECG screening for AF in both control subjects and stroke patients may explain the disparity between our findings and the findings of the RIKS-Stroke study in which AF incidence was four times higher in stroke patients than in the general population.

CHADS₂ and CHA₂DS₂-VASc scores associated with atrial fibrillation

History of AF prior to ischemic stroke was independently associated with age, cardiac failure (Study I) and vascular diseases (Study III), while hypertension independently predicted the development of AF during the 10-year follow-up after the first-ever ischemic stroke (Study IV). All these clinical risk factors are included in the risk scoring system for predicting cardioembolic strokes in patients with AF. The association of high

cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc scales with AF developing has been demonstrated in different cohorts (23, 33, 34). For that reason, we tested these scales to assess their association with the history of AF in ischemic stroke patients and to evaluate their predictive value for new-onset AF after first-ever ischemic stroke.

In agreement with earlier reports (33, 35, 89), in a population of patients with first-ever ischemic stroke, the cardiovascular risk profile expressed as a CHA₂DS₂-VASc score appears to be strongly linked to AF prevalence.

The risk of new-onset AF was related to CHADS₂ and CHA₂DS₂-VASc scores, such that one in three stroke patients with CHADS₂ ≥ 4 or CHA₂DS₂-VASc ≥ 5 had new-onset AF documented during their post-stroke 10-year follow-up. Despite modest sensitivity and specificity, low scores, particularly CHA₂DS₂-VASc, had very high negative predictive value. They may therefore be considered in assessing AF risk after ischemic stroke, and they may affect the AF screening strategy choice.

While the highest AF detection rate after ischemic stroke has been reported in studies with incertable cardiac monitors (81, 82, 90), that strategy is limited in clinical practice due to its invasiveness and high cost. From the healthcare perspective, it is very important to identify the high-risk group of stroke patients who would derive the most clinical benefit from AF detection by prolonged ECG monitoring using implantable devices.

The conventional CHA₂DS₂-VASc score appears to be useful instrument in this context, as supported by our findings.

ECG characteristics associated with atrial fibrillation

One of the most widely studied markers of atrial conduction is P-wave duration. P-wave duration prolongation reflects atrial remodeling predisposing to occurrence of AF. In the Mayo Clinic cohort (Study III), stroke patients with a history of AF had longer P-wave duration than did patients without AF at stroke onset. Another marker of atrial myopathy – P terminal force in lead V1 – was greater in patients with a history of AF than in patients without AF. However, only P terminal force in lead V1 greater than 40 mm*ms was significantly and independently associated with history of AF in stroke patients.

In the LSR cohort, PR interval was independently associated with AF history prior to first-ever ischemic stroke, which is in agreement with published data (91, 92). A prolonged PR interval may reflect atrial conduction disturbances associated with AF. On the other hand, medication-induced prolongation of the PR interval is not rare in patients with AF treated with beta-blokers or other rhythm- or rate-control medications affecting atrio-ventricular conduction. In the retrospective register-based study, information on medical treatment was not collected and adjustment for drug usage could not be made during multivariate logistic regression analysis. For that reason, we

cannot consider the PR interval to be a strong marker of underlying AF in our study population.

No ECG characteristic was predictive of short AF episodes detected after ischemic stroke by ECG monitoring in patients without history of AF. The absence of association between post-stroke AF detection and P-wave characteristics may be due to the fact that P-wave abnormalities are a later finding in atrial abnormality progression than LAVI enlargement, and patients without AF at stroke onset did not have advanced atrial remodeling.

No P-wave characteristic was predictive of new-onset AF during the 10-year follow-up after first-ever stroke in the LSR population (Study IV). In contrast to our data, recently published meta-analysis from the Framingham Heart Study (FHS) and the Atherosclerosis Risk in Communities (ARIC) Study (41) showed the link of maximum P-wave duration and maximum P-wave area with a 10-year risk of AF in both patient cohorts. However, P terminal force in lead V1 was associated with the risk of AF in the ARIC cohort and was not predictive of AF in the FHS cohort. The difference was explained by a different design of the two studies as well as by smaller study sample size in the FHS study. The negative findings in the present study may be explained by two reasons. On the one hand, the size of the sample in our study was smaller than in FHS and ARIC studies. On the other hand, patients in the LSR study were older than patients in the FHS and ARIC studies, and perhaps had underlying asymptomatic AF that became apparent during follow-up; in which case P-wave indices as markers of atrial remodeling did not have predictive value for the new-onset AF during follow-up.

Surprisingly, we found an association between QRS duration and the development of AF after ischemic stroke. There is a lack of literature data on the association between QRS characteristics and the risk of AF in ischemic stroke patients. However, it has been shown that in patients without structural heart disease, an incomplete right bundle branch block was a marker for lone AF (93). One possible explanation for that finding was that an incomplete right bundle branch block may be an early sign of fibrosis in the Purkinje system as a marker of the “physiological age” of the conduction system, including atrial tissue. An association between QRS duration and the risk of AF was found (94) in patients with left ventricular dysfunction. QRS duration may reflect myocardial fibrosis due to underlying cardiovascular disorders. Myocardial fibrosis exists both in the ventricular and the atrium, and may be a substrate for AF development.

However, considering the level of significance of QRS association with new-onset AF observed in the study (p value 0.049 in multivariate Cox regression model), this association needs to be interpreted with caution unless confirmed by other data.

Echocardiographic parameters associated with atrial fibrillation

Left atrial dilatation measured as increase in LAVI may be a marker of underlying structural changes in the atrium leading to the development of AF in patients without advanced cardiovascular disorders. It has been shown that LAVI was associated with first-ever ischemic stroke in patients without previous AF (95). One possible explanation for this association is that blood stasis and thrombus formation may occur more often in a left atrium of increased size even when AF is not present (96). Another possible explanation is that these patients had undetected paroxysmal AF that was not present at the time of stroke. Inflammation and structural changes may be more important in the development of atrial remodelling than atrial fibrillation. The CHADS₂ and CHA₂DS₂-VASc scores predict the risk of death or stroke regardless of AF history (97).

Increased LAVI reflects remodelling of the left atrium due to pressure or volume overload (43) and correlates with the extent of left atrial fibrosis (44). Both atrial remodelling and atrial fibrosis are pathological changes associated with the development of AF.

It has been shown that LAVI has a high diagnostic accuracy for paroxysmal AF (45) and can be used in routine clinical practice as a valuable index for selecting patients for continuous ECG monitoring for the purposes of AF detection. In the present study, LAVI < 40 mL/m² has a high negative predictive value for ruling out short AF episodes on ambulatory ECG monitoring. This approach may decrease the number of patients undergoing ambulatory ECG monitoring after stroke, thus reducing healthcare costs for this patient population. Patients with LAVI > 40 mL/m², on the other hand, are more likely to have episodes of asymptomatic AF and should be screened for AF more thoroughly.

In our study, LAVI was also associated with a history of AF independent of other TTE characteristics, and was higher in patients with a history of AF than in patients with short AF episodes. While the difference was not significant (likely due to the small number of patients with detected post-stroke AF), we observed a trend of gradual LAVI increase: LAVI was lowest in patients without any AF, intermediate in patients with short AF episodes, and highest in patients with a history of AF. This trend may reflect the underlying progression of structural changes in the left atrium in patients who develop AF.

LAVI as a marker of structural left atrial remodeling was significantly associated with a history of AF and had strong predictive value for incident AF, thus demonstrating the superiority of LAVI over ECG indices. Future studies could perhaps determine whether increased LAVI alone may predict which patients meet the criteria for initiating oral anticoagulation therapy.

Clinical types of atrial fibrillation

An important finding of this thesis is that the clinical AF type, i.e. permanent vs. recurrent, plays a role in prognosis and in oral anticoagulation therapy effect, which is in contrast with the approach commonly used in guiding documents - namely, treating AF as one entity without clinical type differentiation.

In our study, the recurrent AF in stroke patients was higher than the previously-reported 6% - 44% (7, 49, 50): in our study, it was 60%. The difference was perhaps due to greater availability of historical ECGs, which allowed us to detect additional cases of paroxysmal AF. Our results are supported by other recent studies that used dedicated AF screening methods during the follow-up period. Those studies reported similar paroxysmal AF detection rates (51, 52).

Recent reports suggest that ischemic stroke incidence is similar in patients with paroxysmal AF and permanent AF (47), and that paroxysmal AF carries a risk of thromboembolic complications similar to that of permanent AF (48). Similar stroke incidence in patients with different types of AF may be due to the fact that, while patients with paroxysmal AF are younger and healthier (and thus expected to suffer fewer strokes), patients with permanent AF received OAC therapy more often than patients without permanent AF and therefore had better protection against cardioembolic stroke (47).

Some studies suggested that paroxysmal AF is associated with less severe strokes than permanent AF (49-51). These findings were not verified as differences in NIHSS scores between permanent and recurrent AF were not significant; however, the median NIHSS score in the entire LSR population was lower than previously reported (49-51). Contrary to these findings, the LSR study population was comprised strictly of patients with first-ever ischemic stroke, which may explain the lower stroke severity score in the present study as compared to earlier-reports.

Previously, a more favourable outcome was demonstrated for paroxysmal AF vs. chronic AF at discharge after ischemic stroke (50). In contrast, in the LSR population, higher in-hospital mortality was found for patients with recurrent AF vs. patients with permanent AF. A possible explanation for this result is that, while patients with paroxysmal AF are considered to be younger and healthier, patients with permanent AF received OAC therapy more often and thus had better protection against cardioembolic stroke (47). In the LSR population with AF, the rate of OAC usage at stroke onset was generally low. It was higher in patients with permanent AF, but the difference was not significant.

Literature on the association between clinical types of AF and mortality during long-term follow-up after ischemic stroke is sparse. One study reported that patients with paroxysmal AF have lower mortality rates than patients with persistent and permanent AF during the 10-year follow-up after ischemic stroke (51). The present study showed that stroke patients with AF had higher mortality during the 10-year

follow-up than stroke patients without AF, and one of the main findings was that prognosis is worse for patients with permanent AF than for patients with recurrent AF.

While some recent reports have suggested that ischemic stroke incidence appears to be similar in patients with paroxysmal AF and permanent AF (47) and that paroxysmal AF carries a risk of thromboembolic complications similar to permanent AF (48), other studies suggest that paroxysmal AF is associated with less severe strokes than permanent AF (49-51). One possible explanation is that hemodynamic and hemostatic abnormalities (which are more profound in permanent AF than in paroxysmal AF) play an important role in ischemic stroke development (49). It has been suggested that, in patients with paroxysmal AF, hemostasis abnormalities appear to be related to the duration of AF paroxysms (98). More profound hemostatic disturbances and hemodynamic abnormalities in patients with permanent AF may be related to stroke severity due to relatively larger thrombi formation in those patients vs. patients with paroxysmal AF, causing infarcts of bigger volume and influencing the post-stroke prognosis.

Stroke severity may explain the worsened prognosis for patients with permanent AF than for patients with paroxysmal AF. However, in our study, stroke severity measured by the NIHSS scale was similar for patients with recurrent AF and permanent AF. We found that patients with recurrent AF did not differ from patients with permanent AF in the prevalence of diabetes mellitus, cardiac failure, hypertension and vascular disease. This is in contrast to a study showing more favorable outcomes 6 months after stroke for patients with paroxysmal AF. In that study, patients with permanent AF had a higher proportion of cardiac failure and diabetes mellitus (49). In the present study, the only difference observed related to age: patients with permanent AF were older than patients with recurrent AF. In the multivariate Cox regression model, age was an independent predictor of mortality, in agreement with earlier data (24). However, even after adjustment for age, AF still remained an independent predictor of mortality, with permanent AF having the highest impact on outcomes.

Oral anticoagulant therapy

According to current guidelines for managing atrial fibrillation, all stroke survivors have a CHA₂DS₂-VASc score of at least 2, and therefore stroke survivors with AF have an indication for OAC treatment (6). Since our study population was recruited before novel anticoagulants were available, OAC therapy included only the vitamin K antagonist – warfarin. Underuse of the vitamin K antagonist is well-known (99, 100). In our study, only 45% of stroke patients with AF received OAC therapy after discharge, while 51% were prescribed antiplatelet medications and 4% received no antithrombotic treatment. Our data are in line with recently-published data (101) showing that elderly patients with AF were prescribed vitamin K antagonist in 39% of cases, antiplatelet medications in 40% of cases, and no antithrombotic therapy was

prescribed in 10% of cases. In that study, during a mean follow-up of 1.5 years, all-cause mortality was lower in patients treated with OAC than in patients treated without OAC. The impact of antiplatelet therapy on prognosis was not analyzed separately. However, in the ACTIVE W substudy of stroke-free patients with AF, similar incident rates of ischemic stroke were reported for patients receiving OAC and patients receiving dual antiplatelet therapy (48). In our study, AF patients discharged on one antiplatelet agent had better survival rates than AF patients without antithrombotic therapy but worse survival rates than AF patients treated with OAC.

The benefit of the OAC therapy for patients with AF and who are at risk of thromboembolic complications is well-established (6, 54), and our data support those findings. However, little is known about the long-term prognosis for ischemic stroke patients and different clinical types of AF treated with OAC. A recently published subanalysis of the ROCKET-AF study (55) in which one-third of patients had a stroke in the past reported that patients receiving anticoagulation therapy with persistent AF have a higher risk of thromboembolic events and death than patients with paroxysmal AF. This was seen in patients treated with warfarin as well as in patients treated with rivaroxaban. In agreement with that subanalysis, our study showed that stroke patients with recurrent AF who were receiving OAC had better survival than patients with permanent AF who were receiving OAC. These data may have an important implication for managing patients with AF, especially patients in whom bleeding risk must be balanced with the an expected benefit of anticoagulation therapy.

Surprisingly, stroke patients with recurrent AF who received OAC therapy had the same prognosis as stroke patients without AF, although AF had been proven to increase mortality rates after ischemic stroke (102). One possible explanation of this finding is that patients with recurrent AF have not yet developed advanced cardiac remodeling and therefore have less profound hemostatic disturbances and hemodynamic abnormalities that can be efficiently controlled by OAC. A worse prognosis for patients without OAC therapy was observed regardless of AF clinical type.

Conclusions

- Pre-stroke prevalence of AF appeared to be very high and is strongly associated with the high cardiovascular risk profile measured by the CHA₂DS₂-VASc scale. A comprehensive approach to AF screening through electronic ECG archives allows detecting AF in one-third of patients admitted with first-ever ischemic stroke.
- Despite high specificity, AF diagnosis in the Swedish National Patient Register has modest sensitivity, which may result in underestimating prevalent and incident AF cases by at least 20% if only register data are used for identifying subjects with AF in epidemiology studies.
- LAVI is the strongest independent predictor of paroxysmal AF detected after ischemic stroke, and thus LAVI may be considered to be an early marker of asymptomatic AF in stroke patients without history of AF and advanced structural changes in the heart. Stroke patients with LAVI < 40 mL/m² are less likely to develop paroxysmal AF on prolonged ambulatory ECG monitoring.
- High CHADS₂ and CHA₂DS₂-VASc scores (but not baseline ischemic stroke) predict new-onset AF during follow-up and may identify ischemic stroke survivors with an increased likelihood of developing AF after stroke. These patients may become the target group for dedicated AF screening.
- All-cause mortality was independently associated with the presence of AF, and mortality rates were higher for patients with permanent AF. Stroke patients with recurrent AF who were receiving OAC therapy had the most favourable outcomes, similar to stroke patients without AF and significantly better than OAC-treated stroke patients with permanent AF.

Generally, ischemic stroke survivors with a high CHA₂DS₂-VASc score may be the target group for continuous AF screening and initiation of OAC therapy upon AF detection.

Summary in Swedish

Varje minut drabbas någon av stroke. En av de vanligaste orsakerna till stroke är förmaksflimmer, som ökar risken för att det skall bildas proppar i vänster förmak, vilket i sin tur kan leda till stopp i blodflödet till delar av hjärnan. Behandling med blodförtunnande läkemedel kan minska strokerisken men enligt gällande rekommendationer måste man först påvisa förekomst av förmaksflimmer för att kunna motivera insättning av läkemedel som annars förknippas med en betydande blödningsrisk. Att dokumentera förmaksflimmer kan dock vara en utmaning eftersom sjukdomen i många fall är asymtomatisk eller attackvis påkommande. Därför är det viktigt att hitta pålitliga markörer som på ett kostnadseffektivt sätt kan identifiera patienter med hög risk att utveckla förmaksflimmer som kan bli målgrupp för riktad screening för förmaksflimmer.

Syfte med avhandlingsprojektet har varit att studera prevalensen av förmaksflimmer, dess kliniska varianter och betydelse för långtidsprognosen hos patienter med förstagångsstroke.

Patienter som, enligt Lund Stroke Register, drabbades av ischemisk stroke år 2001-2002 inkluderades i projektet och följdes upp i minst tio år. Ytterligare en kohort av patienter med stroke inkluderades från Mayo-kliniken (Rochester, MN, USA) för att analysera förmaksflimmerdetektion med hjälp av långtidsmonitorering av hjärtrytm tidigt efter stroke.

Förmaksflimmerdiagnostik och bedömning av hälsostatus inklusive utfall vid långtidsuppföljning baserades på genomgång av patienternas journaler, EKG förvarade i den elektroniska EKG-databasen och information om diagnoser från Patientregistret och Dödsorsaksregistret. Uppgifter om behandling med antitrombotiska läkemedel för prevention av strokerecidiv inhämtades från sjukhusets i Lund databas.

Prevalensen av förmaksflimmer visade sig vara 32,4% bland patienter som insjuknar med ischemisk stroke för första gången i sitt liv. Förstoring av vänster förmak, något som kan upptäckas med ultraljudundersökning, visade sig med hög precision kunna identifiera patienter med förmaksflimmer tidigt efter stroke. Däremot kunde inte EKG-markörer med säkerhet peka ut patienter med förmaksflimmer. Vid långtidsuppföljning utvecklade en del patienter förmaksflimmer. Vi har påvisat att benägenheten att utveckla förmaksflimmer på lång sikt kan bedömas med hjälp av samma riskbedömningskala som används för beräkning av strokerisk. Det tyder på att en subgrupp av strokepatienter med hög recidivrisk kan dra nytta av behandling med blodförtunnande läkemedel utan att nödvändigtvis behöva påvisa förekomst av förmaksflimmer. Denna hypotes behöver dock bekräftas i ytterligare studier.

Slutligen har vi påvisat att den kliniska typen av förmaksflimmer, dvs permanent eller icke-permanent, kan spela stor roll för långtidsprognosen och effekten av

antitrombotisk behandling efter stroke. Patienter med den permanenta typen av förmaksflimmer löper den största risken att dö efter ischemisk stroke medan patienter med attackvis påkommande förmaksflimmer som behandlas med antitrombotiska medel har samma prognos som patienter utan arytm.

Vi har således påvisat att en bedömning av risken att utveckla förmaksflimmer och detektering av asymptomatiska former av förmaksflimmer hos patienter med ischemisk stroke är möjlig och viktig för förbättring av prognosen och minskning av risk för strokerecidiv. Både icke-invasiva diagnostiska metoder och välkända och lätt använda riskbedömninginstrument kan användas för bedömning av benägenheten att utveckla förmaksflimmer och på så sätt identifiera den patientgrupp som lämpar sig bäst för dedicerad arytmscreening.

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Paper I

Documentation of atrial fibrillation prior to first-ever ischemic stroke

Baturova MA, Lindgren A, Shubik YV, Olsson SB, Platonov PG. Documentation of atrial fibrillation prior to first-ever ischemic stroke. *Acta Neurol Scand* 2014; 129: 412–419.
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Objectives – We assessed the prevalence of atrial fibrillation (AF) prior to first-ever ischemic stroke by examining a comprehensive electronic ECG archive. **Methods** – The study sample comprised 336 consecutive stroke patients (median age 76 (IQ16) y, 200 men) enrolled in Lund Stroke Register from March 2001 to February 2002 and 336 age- and gender-matched controls without stroke history. AF prior to admission was studied using the regional electronic ECG database and record linkage with the National Swedish Hospital Discharge Register (SHDR). Medical records were reviewed for AF documentation and CHA₂DS₂-VASc risk score. **Results** – Atrial fibrillation before or at stroke onset was detected in 109 (32.4%) stroke patients and 44 (13.1%) controls, $P < 0.001$. Twenty-five of 109 stroke patients had AF detected only on previous ECG ($n = 14$) or through the SHDR ($n = 11$). The most prevalent type of AF in stroke group was non-permanent AF (59.6%). AF prevalence among patients admitted with sinus rhythm at hospital admission ($n = 266$) was higher in those with CHA₂DS₂-VASc score ≥ 6 (28.6%) than with CHA₂DS₂-VASc score < 6 (13.0%), $P = 0.043$. **Conclusion** – Comprehensive approach for AF screening allows detecting AF in one-third of patients admitted with first-ever ischemic stroke. Patients with high cardiovascular risk are more likely to have non-permanent AF.

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Key words: atrial fibrillation; ECG; first-ever ischemic stroke; stroke register

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Introduction

Atrial fibrillation (AF) is an established risk factor for ischemic stroke (1). However, a substantial proportion of patients with ischemic stroke have underlying paroxysmal AF that may not be apparent at admission with ischemic stroke (2). Conventional 24-h Holter ECG monitoring have low sensitivity for AF detection (3, 4), whereas repeated ECG registration after stroke and prolonged Holter ECG monitoring improves AF detection rate (5–8) but may be cumbersome to perform in clinical practice. In these studies, the first episodes of AF were documented after stroke. However, one also cannot completely rule out the possibility of electrophysiological changes in the heart appearing as a consequence of ischemic stroke (9). Rather high prevalence of subclinical AF prior to developed ischemic stroke has

been reported for patients with implanted devices (10). However, the data about prestroke AF prevalence in ischemic stroke populations are sparse.

ECG screening through hospital or regional ECG archives has been shown to be helpful in verification of AF diagnosis (11).

We aimed to assess the prevalence of AF in first-ever ischemic stroke patients prior to stroke using ECG screening through an electronic ECG archive as well as by examining the National Swedish Hospital Discharge Register (SHDR).

Materials and methods

Study cohort

The study sample was collected from the Lund Stroke Register (LSR) and comprised 336 first-ever ischemic stroke patients included between

March 1, 2001 and February 28, 2002 (median age 76 (interquartile range (IQ)16) years, 136 women).

Lund Stroke Register is a prospective, epidemiological register that covers Lund University Hospital catchment area (eight municipalities with 234505 inhabitants as of December 31, 2001) (12). Patients with all first-ever-in-life strokes, including ischemic, hemorrhagic stroke, and subarachnoid hemorrhage were enrolled in LSR when stroke was diagnosed in accordance with WHO definition (13) and confirmed by CT/MR/autopsy examination of the brain. After CT/MR/autopsy, the stroke was defined as ischemic, hemorrhagic stroke, or subarachnoid hemorrhage (14). In this study, only patients with ischemic stroke were included. Control subjects were randomly selected from the same geographical region and matched to LSR cases for the year 2001 by age and gender in a 1:1 case-control manner using the Swedish Population Register (12).

Informed consent was obtained from all participants included in the LSR. The study was approved by the regional Ethics Committee.

Ascertainment of prevalent atrial fibrillation and its clinical types

Information about AF before or at admission for acute ischemic stroke (stroke group) or enrollment in the register (control group) was obtained from electronic medical records, ECG recordings retrieved from the regional electronic ECG database (GE MUSE, GE Healthcare Sverige AB, Danderyd, Sweden) and by record linkage with the SHDR.

The regional ECG database contains all ECGs taken in the Skåne University Hospital, Lund catchment area, including primary care facilities, starting from 1988. All ECGs of study subjects recorded from 1988 until the time of inclusion in the study were reviewed by trained cardiologists (MB and PGP) for the presence of AF prior to inclusion. On surface ECG, AF was defined as a rhythm disorder with irregular RR intervals, indistinct *P*-waves and atrial cycle length of <200 ms in case of distinct atrial activity visible on surface ECG (15). For the purpose of statistical analysis, atrial flutter was considered equal to AF.

Atrial fibrillation diagnosis was also examined by record linkage with the SHDR, which is administered by the Swedish National Board of Health and Welfare. The SHDR includes data on main and secondary diagnoses at discharge from all public hospitals in Sweden since 1987. The

register uses the International Classification of Disease (ICD) codes, with the eighth edition (ICD-8) used until the end of 1986, the ninth edition (ICD-9) between 1987 and 1996, and the 10th edition (ICD-10) from 1997 and onwards (16). AF was defined as presence of any of the following ICD codes: 427.92 for ICD-8, 427D for ICD-9 and I48 for ICD-10 (16). The first date of any above-mentioned ICD codes before or at inclusion was considered as documentation of AF history at baseline.

Atrial fibrillation clinical types were categorized as permanent or non-permanent (17). AF was defined as non-permanent when it was considered paroxysmal or persistent (with consecutive cardioversion) by the attending physician or when spontaneous conversion to sinus rhythm was proven by the ECG with sinus rhythm at inclusion. Patients who had AF diagnosis in the SHDR and had sinus rhythm at admission were considered having non-permanent AF. Permanent AF was diagnosed in accordance with documentation in medical records, or when serial ECGs demonstrated arrhythmia without intervening sinus rhythm, including admission ECG (11).

Study variables

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) (18). For all study subjects, we evaluated cardiovascular risk profile prior to inclusion using CHADS₂ and CHA₂DS₂-VASc scores (15). The index ischemic stroke was not considered when these scores were calculated.

Oral anticoagulation (OAC) therapy at any time prior to stroke or enrollment 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.

Statistical methods

Groups were compared 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. To identify clinical predictors of ischemic stroke, significantly associated covariates

were further evaluated in univariate logistic regression models with estimation of odds ratios and likelihood-ratio tests. To determine independent predictors of ischemic stroke, clinical factors significantly associated with stroke in the univariate models were subsequently included in a stepwise regression analysis with backwards elimination.

P-values of <0.05 were considered significant. All analyses were performed using SPSS Statistics 20 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

The baseline characteristics are summarized in Table 1. The cardiovascular risk profile (CHA₂DS₂-VASc score) was higher in the stroke group than in the control: patients with ischemic stroke more often had history of CHF (8%, 95% CI 5–11 vs 4%, 95% CI 2–6, *P* = 0.037), hypertension (58%, 95% CI 53–63 vs 34%, 95% CI 29–39, *P* < 0.001), diabetes mellitus (19%, 95% CI 15–23 vs 7%, 95% CI 4–10, *P* < 0.001), IHD (42%, 95% CI 34–52 vs 19%, 95% CI 15–23, *P* < 0.001), and TIA (22%, 95% CI 18–26 vs 1%, 95% CI 0–2, *P* < 0.001) at baseline.

AF detection

Retrospective regional database ECG screening – In total, 3328 ECGs were reviewed for the presence

of AF. The number of available ECG recordings by the time of inclusion in the study was higher in the stroke group, and was highest in patients with AF (Table 1).

Seventy stroke patients (20.8%) had AF on admission ECG; 24 of them (7.1%) did not have any prior documentation or history of AF. In addition, AF was found on at least one historical ECG in 22 stroke patients (6.5%) who presented with sinus rhythm at baseline. Of these, 14 patients (4.2%) did not have a history of prior AF mentioned in their admission medical records. In the control group, AF at any time prior to enrollment was documented in 30 subjects (8.9%).

AF history in medical records – Six stroke patients (1.8%) and two control subjects (0.6%) had AF history documented in medical records even though ECG did not show AF prior to or at inclusion.

AF diagnosis codes in the National Swedish Hospital Discharge Registry – Record linkage with SHDR revealed 11 additional stroke patients (3.3%) and 12 controls (3.6%) with AF diagnosis for whom neither AF ECG was found in the ECG databases nor information about AF was available in medical records.

In total, AF by baseline was diagnosed in 109 patients (32.4%) and in 44 controls (13.1%), *P* < 0.001. (Fig. 1).

AF clinical types – Non-permanent AF was the most prevalent type among stroke patients with

Table 1 Baseline characteristics

Variables	Stroke group			Control group		
	All, <i>n</i> = 336	AF, <i>n</i> = 109	No AF, <i>n</i> = 227	All, <i>n</i> = 336	AF, <i>n</i> = 44	No AF, <i>n</i> = 292
Women, <i>n</i> (%)	136 (41)	44 (40)	92 (41)	136 (41)	22 (50)	114 (39)
Age, median (IQ) years	76 (16)	81 (12)	73 (17)**	77 (15)	83 (9)	75 (15)***
Cardiac failure, <i>n</i> (%)	8 (8)	21 (19)	7 (3)**	14 (4)*	7 (16)	7 (2)***
Hypertension, <i>n</i> (%)	195 (58)	65 (60)	130 (57)	114 (34)*	21 (48)	93 (32)***
Diabetes, <i>n</i> (%)	63 (19)	28 (26)	35 (15)**	23 (7)*	5 (11)	18 (6)
TIA, <i>n</i> (%)	74 (22)	25 (23)	49 (22)	4 (1)*	2 (5)****	2 (1)
Vascular diseases, <i>n</i> (%)	142 (42)	47 (43)	95 (42)	62 (19)*	18 (41)	44 (15)***
CHA ₂ DS ₂ -VASc, median (IQ)	3 (3)	4 (2)	3 (2)**	2 (3)*	4 (1)	2 (2)***
NIHSS score, median (IQ)	3 (6)	4 (12)	3 (4)**	–	–	–
AF at or before baseline, <i>n</i> (%)	109 (32)	109 (100)	–	44 (13)*	44 (100)	–
AF on archive ECG, <i>n</i> (%)	92 (27)	92 (84)	–	30 (9)	30 (68)	–
Permanent AF, <i>n</i> (%)	44 (13)	44 (40)	–	9 (3)	9 (20)****	–
Recurrent AF, <i>n</i> (%)	65 (19)	65 (60)	–	35 (10)	35 (80)	–
Number of ECGs by admission, median (IQ) <i>n</i> per person	3 (6)	6 (11)	2 (4)**	2 (6)*	8 (13)	2 (4)***

AF, atrial fibrillation; IQ, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

The index ischemic stroke was not considered when CHADS₂ and CHA₂DS₂-VASc scores were calculated.

**P* < 0.05 in comparison with stroke group.

***P* < 0.05 in comparison with AF patients in stroke group.

****P* < 0.05 in comparison with AF patients in control group.

*****P* < 0.05 in comparison with AF patients in stroke group.

Atrial fibrillation on ECG prior to stroke

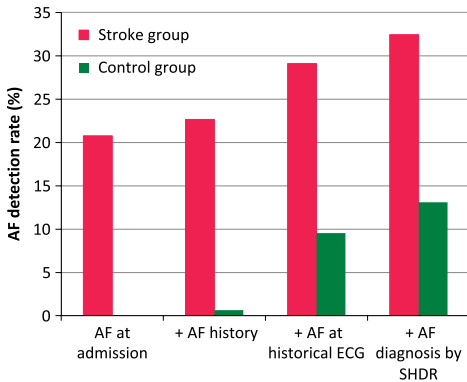


Figure 1. Cumulative detection rate of atrial fibrillation (AF) (%) documented by admission ECG, reviewing medical records for AF history, retrospective ECG screening and record linkage with the National Swedish Hospital Discharge Register (SHDR).

AF (59.6%) and in control subjects with AF (79.5%). Stroke patients with permanent AF were older than stroke patients with non-permanent AF (median age 84 (IQ10) vs 80 (IQ13) years, $P = 0.002$) and had higher CHADS₂ score (median 2 (IQ3) vs 2 (IQ2), $P = 0.039$). Stroke severity measured by the NIHSS scale was not associated with AF type (median score 4 (IQ11) for permanent vs 5 (IQ13) for non-permanent AF, $P = 0.941$). Since permanent AF was revealed in only nine control subjects, no further analysis was performed in the control group.

Among individuals with non-permanent AF, paroxysmal typical atrial flutter without AF by baseline was revealed in three stroke patients and one control subject. Due to the small number of observations, no separate analysis was performed in this subgroup.

The prevalence of AF and cardiovascular risk profile – The prevalence of AF was higher in patients and controls with a higher cardiovascular risk profile measured by CHA₂DS₂-VASc scale (Fig. 2).

In stroke patients admitted with sinus rhythm on ECG ($n = 266$), 14.6% had AF in past history and AF prevalence was significantly higher in those with CHA₂DS₂-VASc score ≥ 6 (28.6%) than with CHA₂DS₂-VASc score < 6 (13.0%), $P = 0.043$.

Clinical factors associated with stroke

In the univariate analyses, ischemic stroke was associated with history of AF, CHF, hypertension,

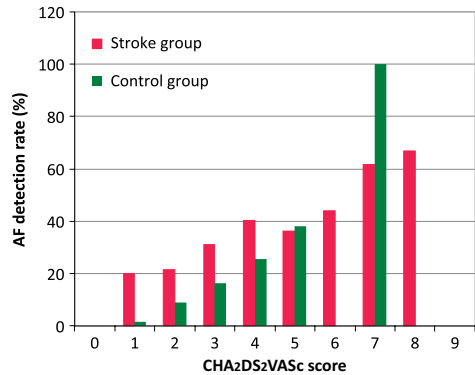


Figure 2. Atrial fibrillation (AF) detection rate (%) in stroke patients ($n = 336$) and controls ($n = 336$) according to CHA₂DS₂VASc score. The index stroke was not included in this score calculation.

diabetes, IHD, and previous TIA. In the multivariate model, history of AF, IHD, diabetes mellitus, hypertension, and TIA remained independently associated with ischemic stroke (Table 2).

Oral anticoagulation therapy

OAC therapy at any time prior to inclusion among patients with AF and indications for secondary prevention therapy (54 stroke patients and 23 controls) did not differ between the stroke and the control groups: 20% vs 26%, respectively, $P = 0.370$. Fourteen patients, among whom there were 10 patients with a known AF, had their first-ever ischemic stroke onset while being treated with OAC. Of those, eight AF patients had CHADS₂ ≥ 2 . Only three of them had INR ≥ 2 at the time of stroke. Three patients had INR < 2 , and for two patients, INR data during stroke admission were not available.

Table 2 Baseline characteristics associated with ischemic stroke in the study population comparing stroke patients and controls

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>P</i> -value	OR	95% CI	<i>P</i> -value
Cardiac Failure	2.09	1.08–4.05	0.029			
AF at baseline*	3.19	2.16–4.71	<0.001	2.55	1.67–3.89	<0.001
Diabetes	3.14	1.9–4.2	<0.001	1.98	1.13–3.45	0.016
TIA	4.84	2.19–8.06	<0.001	4.29	2.56–7.21	<0.001
Hypertension	2.69	1.97–3.68	<0.001	1.89	1.33–2.68	<0.001
Vascular diseases	3.24	2.28–4.59	<0.001	2.27	1.54–3.33	<0.001

AF, atrial fibrillation; CI, confidence interval; OR, odds ratio; TIA, transient ischemic attack.

*AF at baseline – AF diagnosis prior to stroke or at stroke admission.

Discussion

Prevalence of AF detected using a regional ECG database

Our finding of a cumulative detection rate of AF of 32.4% before or at ischemic stroke onset is higher than in previous population-based studies, in which AF was documented at index admission only on the basis of clinical information or admission ECG. Those studies reported an AF prevalence in stroke patients of 20–24.6% (19, 20). Additional repeated conventional snapshot ECG recordings after admission for ischemic stroke appear to increase AF detection rate by 1.4–6.7% (2, 4, 7). The diagnostic yield of 24–48 h Holter ECG monitoring in patients with ischemic stroke and sinus rhythm at admission has been reported to be 1–6.4% (4, 7, 8) and could be increased to 12.5% if the ECG recordings were continued for a week (8). High prevalence of AF in patients with ischemic stroke was also reported in another publication based on data from the Swedish national RIKS-Stroke registry (30.3%) (21). However, these data are based on the information available from the SHDR and not strictly limited to AF detection *prior* to the stroke event. The important difference in our study was that we considered only AF diagnosis established *prior* to or at admission for the stroke event, while a majority of earlier studies include any AF diagnosis also *after* the date of stroke onset.

In agreement with the above-cited reports, 20.8% of stroke patients in our study had AF on ECG at admission. Using only the information available to physicians at the time of admission with stroke, we have shown that a review of historical ECGs allows AF detection in the range comparable to the range reported using conventional 24–48 ECG monitoring. Notably, AF detection rate among age- and gender-matched controls using the same ECG screening approach reached 13.1% in agreement with the data which reported the prevalence of AF detected by stepwise ECG screening 14% in aging Swedish population (22).

The probability of AF being causatively linked to the ischemic stroke event is likely to be higher for AF observed prior to stroke, which is why we focused our analysis on AF history/records prior to admission/enrollment. Most previous studies that reported high prevalence of AF in the stroke population included AF episodes first detected after stroke using dedicated AF screening measures. One also cannot completely rule out the probability of electrophysiological changes in the heart appearing as a consequence of ischemic stroke.

In line with a previous study (23) that reported association between CHA_2DS_2 -VASc score and risk for new-onset AF, our population of patients with first-ever ischemic stroke had a strong relation between cardiovascular risk profile burden – expressed as a CHA_2DS_2 -VASc score – and AF prevalence.

Association between AF clinical type and stroke severity

One of our main findings is the high proportion of non-permanent AF (59.6%) among the total number of stroke patients with AF that exceeds earlier reported 6.3–43.8% proportions (20, 24, 25) and is likely due to availability of the high number of historical ECGs. Our results are supported by recent studies using dedicated AF screening measures during the follow-up period after stroke, which report similar non-permanent AF detection rates (26, 27).

Recent reports suggested that ischemic stroke incidence appears to be similar in paroxysmal and permanent AF (28), and that paroxysmal AF carries a thromboembolic complications risk similar to permanent AF (29). The similar stroke incidence in patients with different types of AF may be due to that, despite patients with paroxysmal AF are younger and healthier (and thereby expected to suffer fewer strokes), patients with permanent AF more often received OAC therapy and therefore had better protection against cardioembolic stroke (28).

Some studies suggest that paroxysmal AF is associated with less severe strokes than permanent AF (24–26). We could not verify these findings, as the differences in NIHSS scores between permanent and non-permanent AF were not significant; however, the median NIHSS score in the entire LSR population that we studied was lower than earlier reported (24–26). Contrary to these reports, our study population comprised patients with first-ever ischemic stroke only, which may explain the lower stroke severity score in our study as compared with earlier reported scores in this context.

Isolated atrial flutter and stroke

The prevalence of typical isolated atrial flutter in our population was 0.9% in the stroke group and 0.3% in the control group, and accounted for 2.6% of all patients with atrial arrhythmias. Literature on long-term stroke risk associated with atrial flutter is sparse, and information on its prevalence in the population is scarce because atrial flutter is often considered together with AF for assessment of its impact on prognosis. In one

report, isolated atrial flutter was present in 1.4% of hospitalized patients, and was associated with only a small increase of stroke risk compared with arrhythmia-free patients, and was lower than in patients with AF (30). Due to the small number of observations, we were unable to establish an association between typical atrial flutter and ischemic stroke; however, the absolute prevalence of isolated atrial flutter in the stroke population appears to be low.

Clinical factors associated with ischemic stroke

Our findings of strong and independent associations of history of TIA, AF, diabetes, hypertension, and IHD with ischemic stroke are in agreement with earlier data (31, 32). The strongest association with ischemic stroke in our study was found for the history of TIA. Low usage of OAC in our study population (20% and 26% treated with OAC prior to enrollment among patients with known AF before inclusion and CHADS₂ score ≥ 2 in the stroke and control groups, respectively) reflects clinical reality at the time of inclusion of these subjects in LSR (33), whereas more recent studies report higher OAC usage in AF patients, up to 80% (34, 35).

Clinical aspects

Notably, even in the control population AF was present to a certain degree, while only a minority of these patients with AF used OAC at any occasion. Even more startling, OAC was only used in 6 of 23 who had a CHADS₂ score of 2 or more. It is therefore obvious that a retrospective analysis of ECG from individuals of the current ages, who have never suffered stroke, may help to identify a cohort which rightly ought to be given OAC. Together with the increasing evidence for benefit by stroke protection using OAC the observation also supports the idea of prospective search for individuals with undetected AF.

Study limitations

The number of ECGs available for analysis was lower in the control group, with control group participants reflecting generally better health status and lower need for contact with health care providers than those in the stroke group. This may lead to an underestimation of AF prevalence in the control group that would mainly affect detection of asymptomatic AF. Also, we have not been able to account for patients' mobility between different geographical regions, as our

ECG search was limited to the ECG database that covers the Skania region of Southern Sweden, thus making possible additional ECG registrations made in the rest of Sweden unavailable for review.

It should also be kept in mind that despite covering public sector healthcare facilities, the regional ECG collection and storage system does not provide full coverage, thus not capturing all ECGs recorded by non-public health entrepreneurs. Though limited in number during and prior to the time when our study material was collected, non-inclusion of private primary care facilities may have additionally contributed to possible underestimation of the actual AF detection rate.

Finally, the study was performed in a single hospital with a moderate sample size that makes data more vulnerable to variations and factors influenced by chance.

Conclusion

Prestroke prevalence of AF appeared to be very high and is strongly associated with the presence of established cardiovascular risk factors. We have shown that AF detection at admission with stroke may be significantly improved by using historical electronic ECG archives that allow establishing of AF diagnosis in patients without clinical history of AF thus bringing up the pre-stroke AF prevalence to the level comparable with earlier reported in studies that used dedicated AF screening during follow-up after stroke.

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Conflict of interests

None of the authors has any conflicts of interest to declare.

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Paper II

Atrial fibrillation in patients with ischaemic stroke in the Swedish national patient registers: how much do we miss?

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Aims

Data from national discharge registers are commonly used to estimate prevalence and incidence of atrial fibrillation (AF) in epidemiology studies. However, sensitivity and specificity of register-based AF diagnosis have not been evaluated. We sought to assess the validity of AF diagnosis in the Swedish Patient Register against electrocardiography (ECG) documentation of AF.

Methods and results

The study sample comprised of 336 patients [median age 76 (interquartile range (IQR) 67–82 years, 136 female] with first-ever ischaemic stroke, enrolled in the Lund Stroke Register from March 2001 to February 2002 and 1:1 age- and gender-matched control subjects without stroke from the population register. Data was exported from the patient register in October 2011 (the end of follow-up). Atrial fibrillation documentation by ECG was assessed using an electronic archive containing all ECGs taken in the hospital catchment area starting in 1988. A total of 7247 ECGs were reviewed, with the median number of ECGs per person being 7.5 (IQR 3–15). Atrial fibrillation was detected by ECG in 190 patients; and in 188 patients by linkage with patient register. In most patients, AF was documented first by ECG data, with median time to register diagnosis being 16 days (IQR 3–859). Specificity of AF diagnosis in the Swedish Patient Register was 93%, sensitivity was 80%.

Conclusion

Despite the high specificity, AF diagnosis in the Swedish Patient Register assessed in the population of ischaemic stroke patients and age- and gender-matched control subjects has modest sensitivity, which may result in underestimating prevalent and incident AF cases if only register data are used for identification of subjects with AF in epidemiology studies.

Keywords

Atrial fibrillation • Validity • Swedish Patient Register • Sensitivity • Specificity • Electrocardiography

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population, with a prevalence of at least 3%,¹ which increases with age, reaching 15% in elderly people.² Atrial fibrillation is a major cause of mortality and morbidity due to ischaemic stroke.³ The 'gold standard' of AF diagnosis is electrocardiography (ECG).² However, in population-based studies, national discharge registers are commonly used as a simple and inexpensive data source to identify clinical endpoints. Data from the Swedish Patient Register have been used in epidemiological studies to estimate AF prevalence, incidence, and risk factors for ischaemic stroke.^{1,4,5}

Whether or not national registers provide complete and accurate information about disease prevalence remains unclear. In previous studies, high Swedish Patient Register validity was reported for diagnosis of acute myocardial infarction and congestive heart failure,^{6,7} with lower reported validity for less severe diseases, such as hypertension and lipid disorders.⁸

Literature data on AF diagnosis validity in national registers are sparse, and to our knowledge, only one study assessed validity of AF diagnosis in the Swedish Patient Register.⁹ In that study, validity was shown to be high when estimated in a randomly selected sample of 100 patients with a register-based AF diagnosis, verified by ECG data or by information from medical records.⁹ However,

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What's new?

- Though Swedish Patient Register is widely used for the assessment of atrial fibrillation (AF) prevalence and incidence in epidemiological studies, it is not known to what extent it underestimates AF prevalence. This is the first study in which the sensitivity and specificity of Swedish Patient Register-based AF diagnosis was evaluated against the electrocardiography documentation of AF in an unselected cohort of consecutively enrolled patients with ischaemic stroke and control subjects.
- Despite high specificity, register-based AF diagnosis has modest sensitivity, which results in underestimation of AF prevalence and incidence when only register data are used.
- A time lapse exceeding 6 months between the first ECG documentation and AF registration in the Swedish Patient Register is noted for one-third of patients, and should be considered when interpreting AF prevalence and incidence estimates using only the patient register data.

to the best of our knowledge, there has been no study reporting sensitivity and specificity of AF information contained in the Swedish Patient Register.

In the present study, we aimed to assess AF diagnosis validity in the Swedish Patient Register in an unselected sample of ischaemic stroke patients and matched control subjects consecutively included in the Lund Stroke Register¹⁰ and reported to have a high prevalence of AF through an analysis based on a comprehensive review of ECGs in a regional electronic ECG archive.

Materials and methods

Study cohort

The study sample comprised of 336 first-ever ischaemic stroke patients included in the Lund Stroke Register between 1 March 2001 and 28 February 2002 [median age 76, interquartile range (IQR) 67–82 years, 136 female] and 336 control subjects randomly selected from the same geographical region and matched to stroke cases for the year 2001 by age and gender in a 1 : 1 case–control manner using the Swedish Population Register, as previously described.^{10,11} We followed up all study subjects until 17 October 2011. Data from the Swedish Patient Register regarding AF diagnosis for all included subjects up to this date were also collected. Informed consent was obtained from all participants at enrolment in the Lund Stroke Register. The study was approved by the Lund Regional Ethics Committee.

Atrial fibrillation detection through electronic electrocardiography archive

Atrial fibrillation documentation was based on ECG data obtained from the regional electronic ECG database (GE MUSE, GE Healthcare, MegaCare). The regional ECG database contains all ECGs

taken in the hospital catchment area, including primary care facilities, starting from the year 1988. All available ECG recordings for all study subjects from 1988 until the end of follow-up in 2011 were reviewed by a trained cardiologist for the presence of AF (M.A.B.). On surface ECG, AF was defined as a rhythm disorder with irregular RR intervals, indistinct P-waves, and atrial cycle length of <200 ms where distinct atrial activity was visible on surface ECG.² The first date of ECG with AF was considered to be the date of first ECG documentation of AF.

Atrial fibrillation detection by record linkage with national registers

The Swedish Patient Register is administered by the Swedish National Board of Health and Welfare, and includes data on main and secondary diagnoses at discharge from all public hospitals in Sweden starting in the year 1987. The Swedish Patient Register also includes information about outpatient visits to hospitals. All diagnoses are reported by physicians. The register uses International Classification of Disease (ICD) codes, with the 9th edition (ICD-9) used between 1987 and 1996, and the 10th edition (ICD-10) used from 1997 and until today.^{5,9} For all study subjects, we searched for AF diagnosis by linking the subjects' personal identification numbers to the Swedish Patient Register, starting from 1987 and until the end of our follow-up in 2011. In our study, up to 13 secondary diagnoses were available for study subjects. Atrial fibrillation was defined as the presence of any of the following ICD codes: 427D for ICD-9 and I48 for ICD-10.⁹

Vital status, the date of death, as well as primary and secondary diagnoses at death were determined via linkage with the Swedish Cause of Death Register for all study subjects. The Swedish Cause of Death Register is maintained by the Swedish National Board of Health and Welfare and contains information going back to 1961 and until present. The information is derived from death records, including underlying and up to 20 contributory causes of death coded to the current ICD edition at the time of death. For our study population, ICD-10 was used.^{12,13} Information was gathered starting from the date of admission with ischaemic stroke or enrolment in the study, and until the end of the 10-year follow-up. Atrial fibrillation was defined as the presence of the I48 code from the ICD-10.

The first date corresponding to the AF code was considered to be the date of first AF documentation in the national registers.

Case validation and statistical methods

For all study subjects, we evaluated AF diagnosis using ECG data, data from the Swedish Patient Register, the Swedish Cause of Death Register up to the end of follow-up (17 October 2011), as well as recorded information at index hospitalization with stroke or enrolment in the study. The main survey was performed retrospectively on the entire study population based on information available by the end of follow-up. To assess the impact of data availability for study subjects who died during the 10-year follow-up period ($n = 297$), the analysis was repeated using ECG and the Swedish Patient Register data available at the time of inclusion in the study, when all patients and control subjects were alive. Additional subanalyses were performed in the stroke and control groups separately based on the information available by the end of follow-up to assess the accuracy of AF diagnosis in relation to the ischaemic stroke history. A χ^2 test was used to compare categorical variables, and the non-parametric

Mann–Whitney test was used for continuous variables. *P*-values were calculated using Fisher's exact test, with a two-tailed $P < 0.05$ being considered statistically significant.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for register-based AF diagnosis against ECG data, considered as the 'gold standard' for AF verification.

All analyses were performed using SPSS Statistics 20 (SPSS Inc.).

Results

A total of 7247 ECG recordings were available and reviewed for our study population: 3328 by inclusion in the Lund Stroke Register, and 3919 from the date of inclusion to the end of follow-up. The median number of available ECGs per person was 7.5 (IQR 3–15) and was significantly higher among patients and controls with documented AF than among those without documented AF: 13 (IQR 8–23) vs. 6 (IQR 3–11), $P < 0.001$. The earliest AF documented by ECG was dated 14 March 1989 and the first AF diagnosis in the Swedish Patient Register was dated 12 January 1987.

Until the end of follow-up, AF by ECG could be detected in 190 study subjects, while 185 subjects had AF diagnosis in the Swedish Patient Register and 3 in Swedish Cause of Death Register only, thus bringing the total number of AF cases obtained from national registries to 188 (Figure 1). Due to the low number of AF cases obtained from the Swedish Cause of Death Register only and for the sake of brevity, we have in this report denoted the combined source of diagnostics information from the two national registries as 'Swedish Patient Register' only. Atrial fibrillation diagnosis by both ECG and Swedish Patient Register coincided in 152 subjects. In most cases (86%), AF was first documented by ECG. The median time from the date of first AF on ECG to the date of AF diagnosis in the Swedish Patient Register was 16 days (Table 1). In one-third of subjects with ECG-verified AF diagnosis, the time lapse between the dates of AF ECG documentation and diagnosis exceeded 6 months. Atrial fibrillation was not detected by either ECG or the Swedish Patient Register in 446 individuals. Despite the high specificity of the Swedish Patient Register diagnosis, its sensitivity did not exceed 80%. Positive predictive value, specificity, and sensitivity did not differ between the stroke group and control group; however, NPV was lower in stroke patients (Figure 2, Table 2).

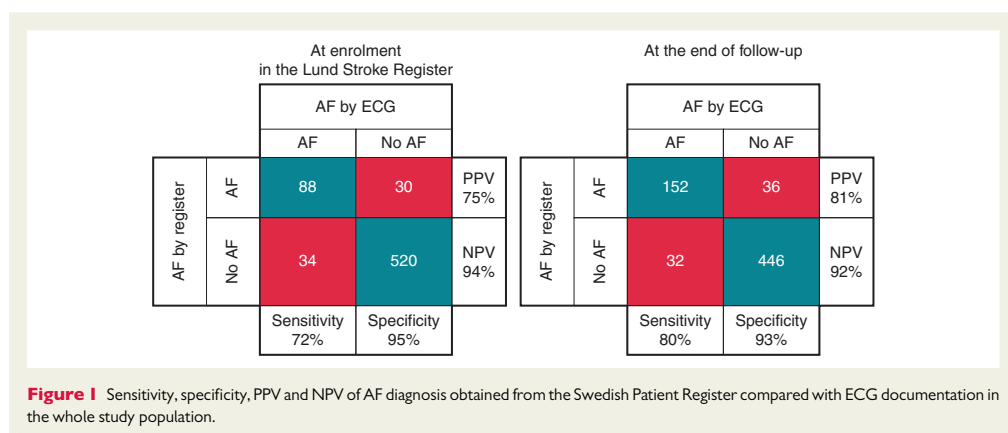


Figure 1 Sensitivity, specificity, PPV and NPV of AF diagnosis obtained from the Swedish Patient Register compared with ECG documentation in the whole study population.

Table 1 Time lapse between ECG and documentation of AF in the Swedish Patient Register

Variable	At enrolment in the study			At the end of FU		
	Total, n = 88	Stroke patients, n = 70	Controls, n = 18	Total, n = 152	Stroke patients, n = 104	Controls, n = 48
First AF documentation by ECG, n (%)	72 (82)	61 (87)	11 (61)	131 (86)	94 (90)	37 (77)
Time lapse between ECG and register diagnosis exceeding 6 months, n (%)	26 (30)	24 (34)	2 (11)	51 (34)	38 (36)	13 (27)
Median time from AF ECG to register diagnosis, days (IQR 25–75%)	10 (1–335)	16 (5–964)	1 (0–6)	16 (3–859)	35 (6–1277)	6 (1–209)

AF, atrial fibrillation; IQR, interquartile range; FU, follow-up. Enrolment of subjects was performed in 2001–02 and the follow-up in 2011.

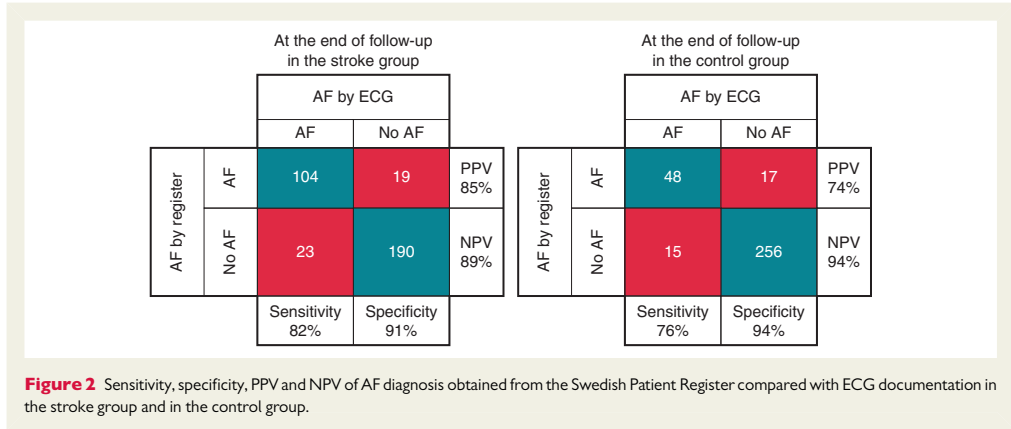


Table 2 Comparison of PPV, NPV, sensitivity, and specificity of AF diagnosis in the Swedish Patient Register between stroke patients and control subjects by the end of follow-up

	All patients, n = 672	Stroke group, n = 336	Control group, n = 336	P-value
PPV, %	81	85	74	0.076
NPV, %	92	89	95	0.033
Sensitivity, %	80	82	76	0.355
Specificity, %	93	91	94	0.236

At inclusion in the Lund Stroke Register, as reported earlier,¹⁰ AF was documented by ECG in 122 study subjects, and by Swedish Patient Register in 118 subjects (Figure 1). Atrial fibrillation diagnosis by both ECG and Swedish Patient Register coincided in 88 subjects, with ECG documentation of AF preceding the Swedish Patient Register diagnosis in most of them. The median time lapse between the date of ECG documentation and the date of ICD code corresponding to AF being entered into the Swedish Patient Register was 10 days (Table 1). As in the main analysis, the time lapse between the first ECG-documented AF and Swedish Patient Register diagnosis exceeded 6 months for about one-third of individuals. Atrial fibrillation was not detected either by ECG or Swedish Patient Register in 520 subjects. Similarly to the analysis performed on the entire dataset at the end of the follow-up, analysis at inclusion in the Lund Stroke Register showed high specificity but relatively low sensitivity of the Swedish Patient Register diagnosis of AF (72%).

No difference was found between estimated values of AF diagnosis validity at inclusion and at the end of follow-up: the P-value for PPV was 0.196, for NPV it was 0.278, for sensitivity the P-value was 0.107, and for specificity it was 0.187.

Discussion

We conducted a validation study of AF diagnosis recorded in the Swedish Patient Register using ECG documentation in the regional ECG database as a 'gold standard'. By reviewing 7247 ECGs, we were able to validate not only the presence of ECG documentation for patients with AF diagnosis in the Swedish Patient Register, but also to assess the specificity and sensitivity of AF diagnosis—which, to the best of our knowledge, has not been reported earlier. One of our most important findings is that using the Swedish Patient Register information to estimate the number of AF cases can result in underestimating the prevalence of AF by at least 20%, which corresponds to the number of subjects in our study who had ECG documentation of AF, yet no AF diagnosis in the Swedish Patient Register.

To the best of our knowledge, our study is the first, in which validity of AF diagnosis in the Swedish Patient Register was assessed using direct ECG verification in a large unselected cohort of consecutively enrolled patients, including subjects both with and without AF diagnosis, thus enabling the assessment of sensitivity and specificity of register-based AF diagnoses. In one recent study,¹⁴ Swedish Patient Register appeared to underestimate AF diagnosis in ischaemic stroke patients by 23% when compared with information on AF diagnosed by primary care facilities. This further supports the importance of access to either ECG documentation or clinical information collected by primary care providers to assess the presence of AF in high-risk patient groups.

Only a small number of studies have addressed the AF diagnosis validation issue in other countries. In a recent Danish study, the PPV for AF diagnosis in the Danish National Patient Registry on a selected sample of 300 patients was reported to be 92% using a combination of ECG and medical record information.¹⁵ In our study, only ECG data were used to confirm AF, which explains why validity of AF diagnosis in the Swedish Patient Register (i.e. PPV) appeared to be lower than previously reported in studies based on combined information sources.^{9,15,16} However, in the Danish study,¹⁵ AF diagnosis was definitely confirmed by relevant documentation in only 229 of 284 patients (81%), which is in line with our findings.

In the present study, we report a lower PPV of register-based AF diagnosis than the 97% we previously reported.⁹ Two main reasons that may explain the difference between the two study results are that, in our previous study, AF diagnosis validation was performed in a randomly selected sample of 100 patients with a positive AF diagnosis by the Swedish Patient Register, including a review of medical records—which was not done in the present study. However, even if only ECG verification was used, the PPV estimated in the present study is still lower than the 95% PPV from our earlier report. The difference may also be due to that the study population in our earlier study⁹ was randomly selected from a prospective epidemiological cohort with a specific, standardized protocol for registration of their health status, and therefore, those study subjects may have been more thoroughly examined and may have more extensive medical documentation, including ECG recordings, than the patients enrolled in the Lund Stroke Register. It is also possible that patients included in the present study might have had ECG recordings showing AF, which were not properly archived and were unavailable for review thus leading to possible underestimation of the number of ECG-confirmed AF cases.

The sensitivity of AF diagnosis in the Swedish Patient Register was found to be 72% at the time of enrolment—this is in agreement with the 71% sensitivity previously reported in the Cardiovascular Health Study.¹⁶ At the end of follow-up in our study, the sensitivity had increased to 80%, but the difference between the two estimates was not significant.

The sensitivity, specificity, and PPV were similar between the stroke patients and the control subjects and were comparable with the data reported for the entire study population, which supports the reliability of these estimates. The only difference was found for NPV, which was lower in stroke population (89%), likely due to a higher prevalence of AF in the stroke patients than in the control subjects.

Despite the high NPV related to the relatively low prevalence of AF in the studied population, the sensitivity of AF diagnosis in the Swedish Patient Register appears to be rather modest, and indicates that the actual number of stroke patients with AF may be at least 20% higher than the number of patients assessed using only the Swedish Patient Register. The underestimation of AF in the Swedish Patient Register can in part be explained by the fact that AF may have been considered as a comorbidity not necessarily present or requiring interventions at the time of hospital admission and for that reason not indicated as a diagnosis. Notably, in our study, AF diagnosis validity appeared to be very similar at two measurements taken 10 years apart and based on nearly twice as many ECGs available for analysis at the end of follow-up as compared with the number of ECGs available at the time of the study subjects' inclusion in the Lund Stroke Register, which supports the reliability of our estimates. Also notable is that ECGs uploaded to the regional archive reflect predominantly symptomatic AF that leads to the patients' contact with healthcare providers—still, the true prevalence of AF in the overall population is likely underestimated. Dedicated AF screening, however, enables the detection of additional cases of asymptomatic or mildly symptomatic AF, as recent studies show.^{17–19}

In our study, we found that ECG diagnosis of AF preceded AF registration in the Swedish Patient Register in most patients, most likely since the first documentation of AF was made at the primary care

level and not in the hospital. While electronic ECG archive covers both primary care facilities and in-hospital units, the Swedish Patient Registry only contains information on patients who were hospitalized, thus explaining the time lapse. In approximately one-third of all cases, the time lapse between the date of the first ECG recording with AF to the date corresponding to AF code being entered in the Swedish Patient Register was longer than 6 months.

The time lapse in AF diagnosis, as described in our study, may result in a situation where the Swedish Patient Register does not provide complete information about AF prevalence at a certain point in time, thus decreasing register data reliability. Nevertheless, our study showed that the median time between the ECG and Swedish Patient Register diagnosis usually did not exceed 3 weeks, which indicates that such a time lapse should not significantly affect the validity of register data. Additional information from outpatient care providers may further improve the validity of register-based identification of patients with AF.

Study limitations

Several issues need to be kept in mind when interpreting our findings. Stroke patients enrolled in the Lund Stroke Register were mostly treated at hospital, and so these patients likely had higher number of ECG recordings and discharge diagnoses recorded in the Swedish Patient Register than subjects recruited from general population. Although our study consisted of an unselected cohort of consecutively enrolled patients, our study sample of patients with ischaemic stroke and matched control subjects may not be representative of the population in general. However, patients with ischaemic stroke are individuals for whom knowledge about prevalent and incident AF is crucially important to assess risk and predict prognosis.

In this study, we did not consider the type of AF (permanent or non-permanent). It is likely that permanent AF is easier to capture on ECG than non-permanent AF, which may have affected AF detection rate in patients with different clinical types of AF. Underestimation of asymptomatic AF is another well-known problem, which is an inherent limitation for population-based studies where information on incident AF is obtained from diagnosis registers. The number of ECGs available for analysis in our study was lower for patients without AF documentation: this could be due to both lack of AF diagnosis and also due to those patients having better health status and thus lesser need to contact healthcare providers than patients with documented AF. Another limitation was that we were unable to monitor the subjects' mobility between various geographical regions, as our ECG search was limited to the ECG database that only covers Southern Sweden's Scania region—thus, ECG registrations possibly made in other regions of Sweden were unavailable for our review.

Although ambulatory ECG recordings taken at hospitals were also available for our review, we cannot claim that we could capture all ambulatory ECGs taken at the primary care level, which might also contribute to underestimation of the AF diagnosis specificity in the Swedish Patient Registry.

Finally, the ECG diagnosis was verified against snapshot 10 s long ECG recordings from electronic archive and we took for granted that the arrhythmia captured on a snapshot ECG should have lasted long enough to be considered as AF. However, this approach

still leaves a possibility, even though rather unlikely, that the duration of AF episode did not reach 30 s required for diagnosis as per current recommendations.²

Conclusion

Despite high specificity and NPV, diagnosis of AF in the Swedish Patient Register has modest sensitivity, which may result in underestimating prevalent and incident AF cases by at least 20% if only register-based information is used to identify subjects with AF in epidemiology studies. A time lapse of more than 6 months for AF registration in the Swedish Patient Register after the first ECG documentation was noted for a significant minority of patients (one-third), and should be considered when interpreting AF prevalence and incidence estimates using only register data.

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Conflict of interest: none declared.

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Paper III

Electrocardiographic and Echocardiographic Predictors of paroxysmal Atrial Fibrillation detected after ischemic stroke.

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Abstract

Background: Detection of atrial fibrillation (AF) after ischemic stroke is challenging due to its paroxysmal nature. We aimed to assess predictors of paroxysmal AF using non-invasive surface ECG and transthoracic echocardiography (TTE) to select candidates for AF screening.

Methods: Ischemic stroke patients without documented AF (n=110, 67±10 years, 40 female) and a control group of age- and gender-matched patients with history of paroxysmal AF prior to stroke (n=55, 67±10 years, 19 female) comprised the study sample. Using non-invasive ECG monitoring during three weeks, short episodes of paroxysmal AF were detected in 24 of 110 patients (22 %). The standard 12-lead ECG with sinus rhythm at stroke onset was digitally processed and analyzed. TTEs were reviewed for these patients.

Results: AF history was independently associated with P terminal force in lead V₁ > 40 mm*ms (OR 4.04 95%CI 1.34-12.14, p=0.013) and left atrial volume index (LAVI) (OR 1.08 95%CI 1.03-1.13, p=0.002). Among patients without AF history, no ECG characteristics were predictive of AF detected after the stroke. LAVI remained an independent predictor of AF after stroke (OR 1.09 95%CI 1.02-1.16, p=0.017). A cutoff of <40 mL/m² had an 84% negative predictive value for ruling out AF on ambulatory monitoring with a sensitivity of 50% and a specificity of 86%.

Conclusion: In a post hoc analysis, left atrial dilatation assessed by LAVI independently predicted AF after stroke in patients without prior AF history while the value of other clinical or ECG markers was limited.

Key words: atrial fibrillation, ischemic stroke, ECG, left atrial volume index.

Introduction

The high prevalence of atrial fibrillation (AF) in ischemic stroke patients is well documented [1, 2]. The detection of AF after ischemic stroke is important, as anticoagulation therapy, as opposed to aspirin, is hence used to prevent recurrent thromboembolic events. However, paroxysmal AF is often underdiagnosed. Routine diagnostic screening techniques, such as 24-hour Holter ECG monitoring, have modest sensitivity for AF detection [3, 4]. Prolonged ECG monitoring increases the detection rate of AF after a stroke [5]; however, the most appropriate AF screening modality for ischemic stroke survivors is not known.

Atrial remodeling predisposing to AF can be demonstrated using available non-invasive techniques such as surface ECG and transthoracic echocardiography (TTE),

which may be used to select candidates for more costly and time consuming, and obtrusive prolonged AF screening.

Frequent supraventricular ectopic activity, including frequent supraventricular premature complexes and supraventricular runs detected by 24-hour Holter ECG monitoring, are predictive of AF [6, 7]. A case-control study using ambulatory ECG monitoring for three weeks after a stroke showed that short episodes of asymptomatic AF are common both in patients with cryptogenic stroke and patients with stroke of known cause [8]. Identification of clinical markers predictive of AF after stroke would facilitate implementation of AF screening in patients at high risk for developing the arrhythmia and optimize the use of health care resources.

We aimed to assess clinical, ECG and echocardiographic characteristics predictive of paroxysmal AF detected using ambulatory ECG monitoring early after ischemic stroke period.

Material and methods

Study cohort

The study cohort was recruited from the cohort of ischemic stroke patients treated at Mayo Clinic (Rochester, MN). Patients without history of AF or atrial flutter prior to or at the index stroke event were compared with those with documented paroxysmal AF by admission with stroke.

Study group of patients without AF history comprised of 110 patients with ischemic stroke either cryptogenic (n=55) or of known cause (n=55) who were previously included in the recently published analysis [8] and who had a surface ECG during sinus rhythm obtained at stroke onset (mean age 67±10 years, 40 female). Using ambulatory ECG monitoring for three weeks (Mobile Cardiac Outpatient Telemetry (MCOT) system - CardioNet, Conshohocken, PA), short AF episodes of median 6 seconds duration (IQR 6-9) were detected in 24 patients (22%). All arrhythmic episodes were manually reviewed by a board certified electrophysiologist. The 24 patients with newly detected short AF episodes after stroke (ShortAF Group) were compared to the 86 stroke patients without detected AF (NoAF Group).

Control group was randomly selected from age- and gender-matched patients treated at Mayo Clinic with ischemic stroke who had history of paroxysmal AF prior to stroke and sinus rhythm on standard 12-lead ECG at admission (PxAF Group, n=55, 67±10 years, 19 female).

The Mayo Clinic Institutional Review Board approved the research protocol.

Baseline assessment

Baseline clinical assessment included demographics, body mass index, comorbid conditions, such as cardiac failure, hypertension, ischemic heart diseases, stroke or transient ischemic attack in the past, diabetes and cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc scales [9].

ECG analysis

Standard clinical 12-lead ECG recordings with sinus rhythm were obtained at enrollment in all study subjects. Digital signals were extracted and stored in a format readable by MegaCare ECG management system (Siemens-Elema, Stockholm, Sweden. Discontinued). Standard clinical measurements, i.e., P-wave duration, QRS duration, corrected QT interval (using Bazett's formula), PQ interval and P-wave terminal force in Lead V1 were obtained from the MegaCare system using the University of Glasgow 12-lead ECG analysis algorithm [10]. P-wave terminal force in Lead V1 was defined as the duration in milliseconds of the terminal (negative) part of the P wave multiplied by its depth in millimeters [11].

P-wave morphology assessment was performed using custom-made software running on MATLAB R2013b (The MathWorks, Inc., Natick, MA) for Linux. The 12-lead ECG was mathematically transformed into orthogonal leads using the pseudo-inverse of the Dower transformation matrix [12]. The orthogonal leads were denoted X (right-left), Y (up-down), and Z (front-back).

QRS complexes were put in different clusters based on morphology (using cross-correlation as a measure of similarity). Only the largest cluster was used in the analysis as a way of removing ventricular ectopic beats and erroneous beat detections.

P waves were extracted using 250 ms wide signal windows preceding each QRS complex. Different clusters of the signal windows were created based on their morphology, where cross-correlation was used for measure of similarity, and Woody's method used to compensate for differences in PQ interval. The largest cluster was averaged and the actual P wave defined by manual setting of the onset and end. The method used is described in detail elsewhere [13-15].

In addition to conventional P-wave indices, we analyzed gross morphology of P-waves using an automatic algorithm [15], which classified orthogonal P waves into types as having positive polarity in leads X and Y and negative, biphasic (-/+) or positive polarity in lead Z. Biphasic (+/-) P-waves in inferior lead Y have been defined as advanced interatrial block with retrograde left atrial activation (IAB).

Echocardiography

Results of clinically indicated TTE were retrieved from patient medical records. TTE examinations were performed at median 1 day (IQ -10.9 to 2.9 months) from the stroke. We assessed the left atrial volume index (LAVI, ml/m²), ejection fraction (EF), estimated right atrial pressure using inferior vena cava size and respiratory variation (mm Hg), right ventricular pressure (mm Hg), left ventricular end-systolic and end-diastolic internal dimensions (mm).

Statistical methods

Clinical characteristics, ECG and TTE parameters were compared between patients from NoAF Group and ShortAF Group 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 alternatively non-parametric tests, as appropriate.

To identify predictors of paroxysmal AF on prolonged ambulatory ECG monitoring, significantly associated covariates were further evaluated in univariate logistic regression models with the estimation of odds ratios and likelihood-ratio tests. Factors significantly associated with occurrence of the short AF episodes on ECG monitoring in the univariate models were subsequently included in a stepwise regression analysis with backwards elimination. The predictive accuracy of determined in multivariate logistic regression models covariates was evaluated using receiver operating characteristic (ROC) curve analysis with calculation of negative predictive value, sensitivity and specificity of the determined parameters.

The group of patients without history of AF prior to or at the index stroke event was compared to those from the PxAF Group. Univariate logistic regression analysis was performed to identify significantly associated covariates with AF history that were further included in a stepwise regression analysis with backwards elimination.

Results

Clinical characteristics associated with history of paroxysmal AF in ischemic stroke patients

PxAF patients had higher proportion of vascular diseases, cardiac failure and higher cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc scales than patients without AF at baseline (Table 1).

Analysis of ECG data showed that P-wave duration, QRS duration, corrected QT interval were longer and P-wave terminal force in lead V₁ was greater in PxAF patients than in patients without AF at stroke. The distribution of different P wave morphologies was similar in the both groups. P-wave morphology with positive P-waves in leads X,Y and biphasic P-wave in lead Z was the most prevalent type in our study cohort.

TTE examination revealed that patients with AF history had lower EF, higher right atrium systolic pressure, larger left ventricular end-systolic and end-diastolic internal dimensions and greater LAVI than patients without AF.

However, in the multivariate logistic regression analysis only vascular diseases (OR 4.10 95%CI 1.32-12.78, p=0.015), P-wave terminal force in lead V1 greater 40 mm*ms (OR 4.04 95%CI 1.34-12.14, p=0.013) and LAVI (OR 1.08 95%CI 1.03-1.13, p=0.002) remained significantly associated with AF prior to stroke.

Table 1.

Clinical, ECG and Echocardiographic characteristics of stroke patients without AF history at stroke onset and patients with history of AF prior to stroke.

Variables	Patients without AF history, n=110	Patients with PxAF, n=55	P value
Mean age, years *	67 ± 10	68 ± 10	0.686
Female, n (%)	40 (36)	19 (35)	0.864
BMI*	29 ± 5	29 ± 5	0.790
P-wave duration, ms *	113 ± 18	120 ± 17	0.021
PR - interval, ms*	172 ± 28	178 ± 35	0.189
P-wave terminal force in lead V1, mm x ms *	24 ± 26	35 ± 33	0.020
QRS duration, ms *	100 ± 17	107 ± 21	0.021
Corrected QTc interval, ms *	430 ± 28	454 ± 34	<0.001
P-wave morphology			0.435
X(+)Y(+)Z(-), n (%)	19 (19)	8 (16)	
X(+)Y(+)Z(-/+), n (%)	60 (59)	32 (64)	
IAB or X(+)Y(+/-), n (%)	2 (2)	3 (6)	
X(+)Y(+)Z(+), n (%)	21 (21)	7 (14)	
Left atrium volume index, ml/m²	35 ± 12	45±12	<0.001
EF, %*	58 ± 12	52 ± 15	0.027
Left ventricular end-systolic internal demension, mm*	33 ± 9	37 ± 10	0.033
Left ventricular end-diastolic internal demension, mm*	49 ± 7	52 ± 8	0.049
Right atrium pressure, mmHg*	6 ± 2	8 ± 5	0.007
Right ventricular systolic pressure, mmHg*	34 ± 10	36 ± 12	0.242
Diabetes, n (%)	18 (16)	12 (22)	0.399
Hypertension, n (%)	84 (76)	41 (75)	0.848
Vascular diseases, n (%)	21 (19)	20 (36)	0.021
Cardiac failure, n (%)	6 (6)	16 (29)	<0.001
CHADS ₂ score *	3.2 ±0.9	3.5 ± 1.0	0.034
CHA ₂ DS ₂ -VASc score *	4.9 ± 1.5	4.9 ±1.5	0.028

* - the results are performed as mean value ± standard deviation

Predictors of short AF episodes detected after ischemic stroke in patients without AF history

Clinical, ECG and TTE data are summarized in the Table 2.

Patients with AF detected on ECG monitoring were older than patients without detected AF with no differences in sex, BMI, cardiovascular comorbidities and cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc scales. They had greater LAVI than those without AF and did not have any differences in other ECG, including P-wave morphology, and TTE characteristics.

Table 2.

Clinical, ECG and Echocardiographic characteristics of stroke patients without AF history at the stroke event.

	NoAF Group, n=86	ShortAF Group, n=24	P value
Mean age, years*	66 ± 10	71 ± 9	0.033
Men, n (%)	55 (64)	15 (63)	1.000
BMI*	31±23	30±6	0.761
P-wave duration, ms*	136 ± 15	143 ± 18	0.232
PR - interval, ms *	175 ± 29	158± 22	0.007
P-wave terminal force in lead V1, mm x ms*	23 ± 24	28 ± 35	0.394
QRS duration, ms *	100 ± 18	100 ± 15	0.962
QTc, ms *	430 ± 28	430 ± 28	1.000
PW morphology			0.570
X(+)Y(+)Z(-), n (%)	16 (20)	3 (14)	
X(+)Y(+)Z(-/+), n (%)	45 (56)	15 (71)	
IAB or X(+)Y(+/-), n (%)	2 (3)	0 (0)	
X(+)Y(+)Z(+), n (%)	18 (22)	3 (14)	
Left atrium volume index, ml/m ²	32±10	42±15	0.007
EF, %	58 ± 12	56 ± 13	0.499
Left ventricular S, mm *	33 ± 9	35 ± 8	0.496
Left ventricular D, mm*	49 ± 7	50 ± 6	0.679
Right atrial pressure, mmHg*	6 ± 2	6 ± 2	0.498
Right ventricular systolic pressure, mmHg*	33 ± 11	36 ± 7	0.490
Diabetes, n (%)	17 (20)	1 (4)	0.115
Hypertension, n (%)	66 (76)	18 (75)	1.000
Ischemic heart disease , n (%)	17 (20)	4 (17)	1.000
Cardiac failure, n (%)	4 (5)	2 (9)	0.604
CHADS ₂ score*	3.2 ±0.9	3.2 ±0.9	0.996
CHA ₂ DS ₂ -VASc score*	4.3 ±1.5	4.5 ±1.4	0.579

* - the results are performed as mean value ± standard deviation

BMI – body mass index

In a univariate regression analysis, detection of short AF episodes after stroke was associated only with age and LAVI. However, LAVI remained the only independent predictor of AF in multivariate regression analysis (Table 3).

Table 3.

Covariates associated with short AF episodes on ambulatory ECG monitoring detected in patients without prior AF history.

Variables	Univariate regression model			Multivariate regression model (adjusted for age)		
	OR	95% CI	P value	OR	95% CI	P value
LAVI	1.08	1.01-1.15	0.017	1.08	1.01-1.15	0.017
LAVI > 40 ml/m²	6.40	1.15-27.91	0.013	6.40	1.15-27.91	0.013
P wave duration	1.03	1.00-1.06	0.082			
QRS duration	1.00	1.00-1.03	0.961			
Corrected QT interval	1.00	1.00-1.02	0.988			
PTF	1.00	1.00-1.00	0.393			
EF	1.00	1.00-1.03	0.493			
LV end-diastolic dimension	1.02	1.00-1.12	0.672			
LV end-systolic dimension	1.03	1.00-1.10	0.488			
Right atrium pressure	1.11	0.82-1.52	0.492			
Age	1.05	1.00-1.11	0.037			
Hypertension	0.91	0.32-2.60	0.859			
Ischemic heart diseases	0.81	0.25-2.69	0.733			
Cardiac failure	1.86	0.35-10.85	0.488			

LAVI – left atrium volume index

PTF – P terminal force in lead V1

EF – ejection fraction

LV – left ventricle

P < 0.05 is considered significant

The area under the receiver operating characteristics (ROC) curve values for LAVI as an indicator of the short AF episodes detected by ambulatory ECG monitoring was 0.698, p=0.041 (Figure 1). A cutoff of <40 mL/m² had an 84% negative predictive value for ruling out AF on ambulatory monitoring with sensitivity 50% and specificity 86%.

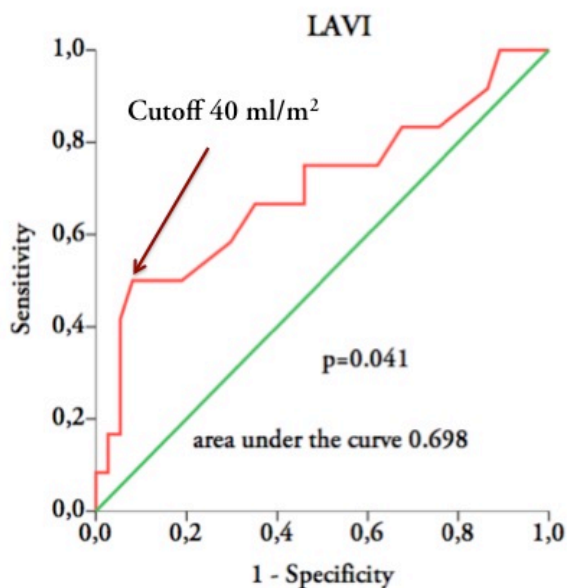


Figure 1. Receiver operating characteristic (ROC) curve for left atrial volume index (LAVI) to detect short episodes of atrial fibrillation (AF) on ambulatory ECG monitoring. Increased LAVI (left panel) has demonstrated significant predictive value for AF detection (optimal cut-off 40 ml/m², specificity 86%, sensitivity 50%, NPV 84%)

Discussion

The main finding is that left atrial dilatation measured by LAVI is the strongest independent predictor of subsequent detection of short AF episodes during prolonged ECG monitoring in patients without AF at stroke onset. ECG data, including P-wave morphology, and underlying comorbidities have a limited value for prediction of paroxysmal AF after ischemic stroke. In patients with known paroxysmal AF, however, a negative terminal deflection in V1 was a potent indicator of arrhythmia. The presence of electrocardiographic abnormalities in patients with known AF, but not in those without such a history suggests that subtle structural changes that are seen by TTE (increased LAVI) develop initially, and that only later are electrocardiographic abnormalities seen

Short episodes of paroxysmal AF

In patients without AF history at stroke onset we have found very short episodes of paroxysmal AF during 3 weeks of ECG monitoring. It is still under discussion whether ultra short AF episodes less than 30 seconds have the same risk of thromboembolic complications as manifested AF [16]. However, it has been shown that supraventricular runs and high supraventricular ectopic activity are predictive of AF occurrence [6, 7]. In ischemic stroke patients premature atrial complexes that occur more frequently than 4 per hour and atrial runs that exceed 5 complexes were associated with the occurrence of paroxysmal AF [17]. The studies with loop recorders implanted for AF screening after ischemic stroke reported the detection of AF lasting 2 minutes or more in average on 48-68 days after implantation [18, 19]. It is likely that, though short episodes of paroxysmal AF were common for our ischemic stroke cohort who underwent ambulatory ECG monitoring for 3 weeks, the monitoring time was not long enough to reveal the full incidence of underlying asymptomatic AF in this stroke cohort. Short episodes of paroxysmal AF might be considered as “surrogates” for prolonged AF that should be used for identification of stroke patients who would benefit from continuous screening for AF.

Whether short episodes of AF indicate the need for anticoagulation therapy remains uncertain. The TRENDS study in patients with implantable devices showed that AF burden exceeding 5.5 hours during any of the preceding 30 days appeared to double the thromboembolic risk [20]. However, in the ASSERT study in patients with implantable devices it has been shown that majority of patients who had stroke while monitored do not have AF at the time and 30 days prior to the stroke onset [21].

As reported recently, early anticoagulation for incident AF and withdrawal after arrhythmia-free periods do not improve outcomes in patients with implantable devices compared with conventional management [22]. Additional studies are needed to investigate the benefit of anticoagulant therapy in patients with short asymptomatic episodes of paroxysmal AF.

Atrial remodeling predisposing to atrial fibrillation

Left atrial volume index

Left atrial dilatation measured as increase in LAVI may be a marker of underlying structural changes in the atrium leading to the development of AF in patients without advanced cardiovascular disorders. Notably, it has been shown that LAVI was associated with first-ever ischemic stroke in patients without previous AF [23]. One possible explanation for this association is that blood stasis and thrombus formation

may occur more often in a left atrium of increased size even when AF is not present [24]. Another possible explanation is that these patients actually have undetected paroxysmal AF, which was not present at the time of stroke. Inflammation and structural changes may be more important than atrial fibrillation. The CHA₂DS₂VASC score increase stroke risk even in the absence of known AF [25].

Increased LAVI reflects remodeling of left atrium due to pressure or volume overload [26] and correlates with the extent of left atrial fibrosis [27]. Both, atrial remodeling and atrial fibrosis, are pathological changes associated with the development of AF.

It has been shown that LAVI has a high diagnostic accuracy for paroxysmal AF [28] and can be used in routine clinical practice as a valuable index to select patients for continuous ECG monitoring for AF detection. We have shown that LAVI < 40 mL/m² has high negative predictive value for ruling out short AF episodes on ambulatory ECG monitoring. This approach might decrease the number of patients undergoing ambulatory ECG monitoring after stroke and consequently reduce costs of care for this patient population. Conversely, patients with LAVI > 40 mL/m² are more likely to have episodes of asymptomatic AF and should be screened for AF more thoroughly.

In our study LAVI was also associated with history of AF independently from other TTE characteristics and was higher in patients with history of AF than in patients with short AF episodes. Though the difference was not significant, likely due to the small number of patients with detected AF after stroke, we observed a trend of gradual LAVI increase from its lowest value in patients without any AF, to intermediate volume in patients with short AF episodes and highest LAVI in patients with history of AF. This trend may reflect the underlying progression structural changes in the left atrium in patients who develop AF.

ECG data

In order to assess ECG predictors of AF detected shortly after ischemic stroke we used ECG characteristics, which were reported to be associated with AF in earlier studies.

One of the most studied markers of atrial conduction is P-wave duration. Its prolongation reflects atrial remodeling predisposing to occurrence of AF. In the Framingham Heart Study the prolongation of P-wave duration predicted the development of AF during long-term follow-up in an elderly community-based cohort [29]. In hypertensive patients, prolonged P-wave duration was associated with AF incidence during 25±3 months [30]. In our study all patients initially had prolonged P-wave duration; however, no association was found between P-wave duration and AF on ambulatory ECG monitoring. These findings are in line with an earlier report of absent association between P-wave prolongation and incident AF among patients with advanced congestive heart failure and prolonged P-waves as baseline in the MADIT-II study [15].

Sinus P-waves with biphasic morphology in the sagittal plane (right precordial leads or orthogonal lead Z) quantified as increase of the negative terminal force in lead V₁ (e.g. P terminal force in lead V₁) was predominately found in the elderly [31], and in patients with a history of AF [32] or structural heart disease [33]. In the Atherosclerosis Risk in Communities study it was found that P terminal force in lead V₁ greater than 4000 $\mu\text{V} \cdot \text{ms}$ was associated with an increased risk of AF [34]. In our study P terminal force in lead V₁ greater than 40 $\text{mm} \cdot \text{ms}$ was independently associated with history of AF in line with the previously reported data.

In summary, while ECG characteristics in patients with established AF and documented arrhythmia prior to stroke expectedly had prolonged P-waves and more prominent P terminal force in lead V₁, none of these ECG characteristics was independently predictive of paroxysmal AF detected in the cohort of patients without prior AF history. Though patients with short AF episodes had longer P wave duration and greater P terminal force in lead V₁, the difference did not reach statistical significance. A plausible explanation for the lack of association between AF detection after stroke and P-wave abnormalities is that most of the patients included in our study had underlying cardiovascular comorbidities and atrial fibrosis affecting P-wave duration and morphology. Another is that P-wave abnormalities are a later finding in atrial myopathy disease progression than LAVI enlargement, and our patients were relatively early in their disease progression.

We cannot completely rule out that the low number of patients with short AF episodes detected after stroke may have undermined our ability to identify an association with P-wave duration and morphology. However, LAVI as a marker of structural left atrial remodeling was significantly associated with history of AF and had strong predictive value for incident AF, thus demonstrating its superiority over ECG indices. Indeed, future studies could determine whether an increased LAVI alone may predict which patients would fulfill the indications for initiation of oral anticoagulation therapy.

Study limitations

The main limitation of our study is the relatively low number of patients who had short AF episodes on ambulatory ECG monitoring, which may affect interpretation of negative findings related to the lack of predictive value of ECG indices for incident AF. Our analysis is also affected by the limitations inherent to its retrospective design. Consequently, our findings should be considered hypothesis-generating and need to be independently reproduced in further studies.

Conclusion

LAVI is the strongest independent predictor of paroxysmal AF detected after ischemic stroke. LAVI might be considered as an early marker of asymptomatic AF in stroke patients without history of AF and advanced structural changes in the heart. Stroke patients with LAVI < 40 mL/m² are less likely to develop paroxysmal AF on prolonged ambulatory ECG monitoring. Use of this cutoff may help determine which stroke patients require more intensive monitoring for AF detection.

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Paper IV



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Predictors of new onset atrial fibrillation during 10-year follow-up after first-ever ischemic stroke[☆]



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ABSTRACT

Background: Paroxysmal atrial fibrillation (AF) may be underdiagnosed in ischemic stroke patients but may be pivotal for initiation of oral anticoagulation therapy. We assessed clinical and ECG predictors of new-onset AF during 10-year follow-up (FU) in ischemic stroke patients.

Methods: The study sample comprised of 227 first-ever ischemic stroke patients without AF (median age 73, interquartile range 25%–75% 63–80 years, 92 female) and 1:1 age- and gender-matched controls without stroke and AF enrolled in the Lund Stroke Register from March 2001 to February 2002. New-onset AF during FU was assessed by screening through regional ECG database and by record linkage with Swedish National Patient Register. The standard 12-lead sinus rhythm ECGs at stroke admission were retrieved from electronic database and digitally processed. Clinical baseline characteristics were studied using medical records.

Results: During FU, AF was found in 39 stroke patients and 30 controls, $p = 0.296$. In stroke patients in multivariate Cox regression analysis AF was associated with hypertension (HR 3.45 CI 95% 1.40–3.49, $p = 0.007$) and QRS duration (HR 1.02 CI 95% 1.00–1.03, $p = 0.049$). High cardiovascular risk was predictive for AF development: for CHADS₂ ≥ 4 HR 2.46 CI 95% 1.45–4.18, $p = 0.001$ and for CHA₂DS₂-VASc ≥ 5 HR 2.29 CI 95% 1.43–3.68, $p = 0.001$. New onset AF was not associated with baseline ischemic stroke: HR 1.46 95% CI 0.90–2.35, $p = 0.121$.

Conclusion: High CHADS₂ and CHA₂DS₂-VASc scores, but not baseline ischemic stroke, predicted new onset AF in FU. QRS duration might be considered a potential risk marker for prediction of AF after ischemic stroke.

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1. Introduction

Though atrial fibrillation (AF) is a very well-known risk factor for ischemic stroke and high prevalence of AF in stroke patients has been reported [1], the impact of ischemic stroke on the risk of development of AF after the initial stroke is not sufficiently clear. Studies with long-term follow-up after ischemic stroke mostly focus on mortality and its

association with clinical predictors of death [2,3] or functional status [4] but do not provide detailed information about occurrence of new AF.

Studies with focus on AF detection after ischemic stroke using ECG monitoring [5,6] do not provide the information about AF developing during long-term follow-up and report rather modest detection rate of AF. Using implantable cardiac monitors (ICM) allows detection of AF up to 36 months after ischemic stroke and increases its detection rate [7]. Though the superiority of ICM-based strategy for AF detection over other ECG monitoring techniques is obvious, its cost effectiveness is largely affected by proper patient selection, which highlights the need for developing AF risk prediction tools.

It has been reported that higher cardiovascular risk profile measured by CHADS₂ was associated with the development of first-ever AF during the first 2 years after stroke [8]. However the usefulness of CHADS₂ and CHA₂DS₂-VASc scales for prediction of AF has also been shown in patients without ischemic stroke [9,10].

Apart from the clinical cardiovascular risk factors, ECG data may be helpful in predicting AF development. Pathologic changes in the atria

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associated with AF may affect atrial depolarization that can be assessed from surface ECG as P wave prolongation or abnormal morphology [11, 12]. It has been shown that P wave duration of >120 ms predicts the development of AF in elderly subjects during long-term follow-up [13]. In patients with left ventricular dysfunction AF has been associated with duration of QRS complex [14].

We aimed to assess usefulness of CHADS₂ and CHA₂DS₂-VASC scales and ECG data for prediction of new onset AF after first-ever ischemic stroke during 10-year follow-up.

2. Materials and Methods

2.1. Study cohort

The original study population was selected from the Lund Stroke Register (LSR) and was comprised of 336 consecutive first-ever ischemic stroke patients included in LSR between March 1, 2001 and February 28, 2002, and 336 control subjects without stroke randomly selected from the same geographical region and matched to LSR cases for the year 2001 by age and gender in a 1:1 case-control manner using the Swedish National Population Register [15]. At enrollment in the LSR, 109 ischemic stroke patients had AF detected by ECG screening, medical records review or record linkage with the Swedish Patient Register as described previously [15] and were excluded from this analysis. The present study sample therefore comprised of 227 first-ever ischemic stroke patients (median age 73 years at stroke onset [interquartile range 25%–75% (IQR) 63–80], 92 females) without AF at inclusion in the LSR. In order to assess the impact of ischemic stroke on AF incidence during long-term follow-up, a comparison was made with 227 age- and gender-matched (median age 73 years [IQR 63–80], 92 females) control subjects selected from the 292 control subjects without either stroke or AF history at enrollment in the LSR from the original cohort [15]. We followed up all study subjects until October 17, 2011.

Informed consent was obtained from all participants included in the LSR. The study was approved by the Lund University Ethics Committee.

2.2. Baseline clinical and ECG assessment in stroke patients

Medical records of all study subjects were analyzed for history of cardiac failure, hypertension, diabetes mellitus, transient ischemic attack (TIA) and ischemic heart disease by baseline. Cardiovascular risk profiles measured by CHADS₂ and CHA₂DS₂-VASC scales [16] were evaluated at the time of inclusion in the LSR in the acute phase when the index ischemic stroke had just occurred.

Sinus rhythm ECG recordings taken at stroke admission with median time from stroke event to ECG registration 0 day (IQR 0–2 days) were extracted from the regional electronic database (GE MUSE, GE Healthcare, MegaCare) and processed offline.

The measurements of P wave duration, QRS duration, corrected QT interval, PQ interval and P wave terminal force in lead V₁ were performed automatically using the University of Glasgow 12-lead ECG analysis algorithm [17]. P wave duration, QRS duration, corrected QT interval and PQ interval were measured in ms. Corrected QT was calculated using Bazett's formula: $QTc = QT/\sqrt{RR}$.

P wave terminal force in lead V₁ was defined as the duration in milliseconds of the terminal (negative) part of the P wave multiplied by its depth in microvolts ($\mu V \cdot ms$).

2.3. Baseline clinical assessment in control subjects

Clinical characteristics at enrollment in the LSR were analyzed for all control subjects. The information about history of cardiac failure, hypertension, diabetes mellitus, TIA and ischemic heart disease was obtained from medical records.

2.4. New onset AF

New onset AF was assessed during the follow-up period starting from the date of enrollment until the end of follow-up or date of death. AF documentation was based on information obtained from the regional electronic ECG archive which contains all ECG recordings taken in hospital catchment area and also by linkage with national registers: Swedish Patient Register and Swedish Causes of Death Register.

All available ECG recordings for all study subjects from the date of enrollment until the end of follow-up in 2011 were reviewed for the presence of AF by a trained cardiologist (MB). On surface ECG, AF was defined as a rhythm disorder which lasted sufficiently long for a 12-lead ECG to be recorded, with irregular RR intervals, indistinct P waves and atrial cycle length of <200 ms where distinct atrial activity was visible on surface ECG [16].

The Swedish Patient Register is administered by the Swedish National Board of Health and Welfare and includes data on main and secondary diagnoses at discharge from all public hospitals in Sweden starting in 1987. The register uses International Classification of Disease (ICD) codes with the 10th edition (ICD-10) used from 1997 and until today [18].

The Cause of Death Register is provided by the Swedish National Board of Health and Welfare and contains information (since 1961) from causes of deaths, including underlying causes of death and up to 20 contributory causes of death coded to the current edition (ICD-10).

The presence of ICD-10 I48 code in the Swedish national registers identified AF diagnosis with high specificity and modest sensitivity as we showed recently in a validation study on patients with ischemic stroke enrolled in the LSR [19].

2.5. Statistical methods

Baseline clinical characteristics were compared between stroke patients and control subjects using chi-square or Fisher's exact test for categorical variables and Student's t-test for continuous variables with an approximately normal distribution or alternatively non-parametric tests, as appropriate.

Endpoint in this study was determined as occurrence of AF. Subjects who did not develop AF during the 10-year follow-up were censored at time of death or at end of follow-up.

Cox proportional hazard regression models were used to estimate the adjusted hazard ratios (HR) and their 95% confidence intervals (CI) of new onset AF associated with clinical and ECG covariates in the stroke group. Univariate Cox regression analyses were performed separately for each component of CHA₂DS₂-VASC score and for each ECG parameter. Clinical factors and ECG parameters significantly associated with new onset AF in the univariate analyses were included in a stepwise regression analysis with backward elimination. The accuracy of CHADS₂ and CHA₂DS₂-VASC scales for AF prediction was evaluated using receiver operating characteristic (ROC) curve analysis with calculation of sensitivity, specificity and negative predictive value of the determined cutoff parameters. The Kaplan-Meier product-limit method was used to generate a survival curve indicating new onset AF during 10-year follow-up after enrollment in LSR.

New onset AF incidence during the 10-year follow-up was compared between stroke patients and control subjects using the Kaplan-Meier product-limit method.

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. Baseline clinical assessment of stroke patients and control subjects

Baseline characteristics at time of enrollment in LSR are summarized in Table 1. Patients with stroke and no AF at stroke onset had increased proportion of hypertension, diabetes mellitus, vascular diseases and history of TIA in the past.

3.2. Detection of new onset AF during 10-year follow-up

During the follow-up (median time 9.4 years [IQR 6.1–9.9]), 115 (51%) stroke patients and 58 (26%) control subjects died ($p < 0.001$). The complete follow-up data were available for 112 (49%) stroke patients and 169 (74%) controls.

New onset AF was found in 69 study subjects (15%): 39 (17%) stroke patients and 30 (13%) control subjects (HR 1.46 95% CI 0.90–2.35, $p = 0.121$, see Fig. 1.)

The median time to AF onset was 3.2 (IQR 1.3–5.9) years.

In total, 2588 ECGs were reviewed with a median number of ECG recordings per person of 4 (IQR 1–8): in the stroke group 1453 ECGs with median number per person 4 (IQR 1–9) and in the control group 1135 ECGs with median number per person 3 (IQR 1–7), $p = 0.041$.

Prior to AF documentation, patients with subsequent new onset AF had ECG registration more often than AF-free subjects: the median number of ECGs per year per person was 0.8 (IQR 0.4–1.6) in patients with subsequent new onset AF, vs 0.4 (IQR 0.1–1) in subjects without detected AF, $p < 0.001$.

Table 1
Baseline clinical characteristics of stroke patients vs control subjects.

Variable	Stroke group, n = 227	Control group, n = 227	p value
Female, n (%)	92 (41)	92 (41)	1.000
Age, median (IQR)	73 (63–80)	73 (63–80)	0.892
Cardiac Failure	7 (3)	5 (2)	0.771
Hypertension, n (%)	130 (57)	74 (31)	<0.001
Diabetes, n (%)	35 (15)	15 (7)	0.004
Vascular diseases, n (%)	95 (42)	30 (13)	<0.001
TIA, n (%)	49 (22)	2 (1)	<0.001

Both stroke patients and controls subjects were free of diagnosed AF at baseline.

IQR – interquartile range 25%–75%.

TIA – transient ischemic attack.

Bold values indicate significance at p value < 0.05.

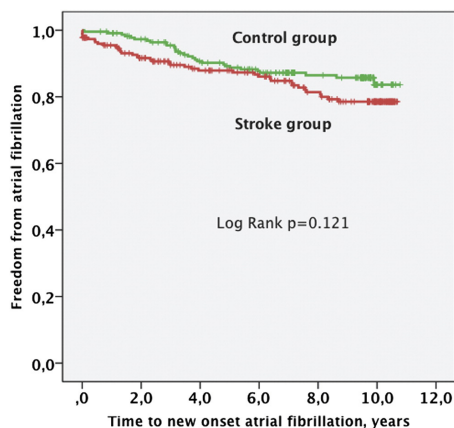


Fig. 1. Kaplan-Meier survival curve indicating new onset AF during 10-year follow-up in stroke patients and control subjects without known AF at baseline.

3.3. Clinical and ECG predictors of new onset AF after ischemic stroke

On admission ECG the median duration of the QRS complex was 96 ms (IQR 88–108), the median duration of the P wave was 116 ms (IQR 106–124), the median duration of the PQ interval – 169 ms (IQR 152–188), the median duration of the corrected QT interval – 435 ms (IQR 418–463). The median P terminal force in lead V₁ value was 2075 $\mu\text{V} \cdot \text{ms}$ (IQR 0–3398).

Analyses of clinical and ECG predictors are detailed in Table 2. In the univariate Cox regression analyses, the incidence of AF during 10-year follow-up was associated with hypertension, cardiac failure, age >65 and QRS duration. However, in the multivariate analysis, only hypertension and QRS duration remained independent predictors of new onset AF.

The areas under the ROC curve values for the CHADS₂ and CHA₂DS₂-VASc scales for prediction of AF occurrence were 0.615 ($p = 0.024$) and 0.606 ($p = 0.037$) respectively. Cutoff value of 3.5 for CHADS₂ scale had sensitivity of 49%, specificity of 68% and negative predictive value of 86%. Cutoff value of 4.5 for CHA₂DS₂-VASc scale had sensitivity of 77%, specificity of 44% and negative predictive value of 90%. High cardiovascular risk was predictive for AF development in the multivariable Cox

Table 2
Clinical and ECG predictors of new onset AF during 10-year follow-up of ischemic stroke patients without known AF at their index stroke.

Variable	Univariate Cox regression analysis			Multivariate Cox regression analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age > 65	2.88	1.20–6.89	0.018	2.56	0.96–6.82	0.059
Hypertension	2.37	1.15–4.86	0.019	3.45	1.40–8.49	0.007
Cardiac failure	4.04	1.24–13.18	0.020			
Diabetes	1.83	0.87–3.87	0.111			
Vascular diseases	1.22	0.65–2.29	0.539			
Female gender	0.78	0.41–1.50	0.459			
QTc interval	1.01	1.00–1.02	0.104			
P wave duration	1.02	0.96–1.05	0.105			
QRS duration	1.02	1.00–1.04	0.025	1.02	1.00–1.03	0.049
PQ interval	1.00	0.99–1.01	0.966			
P terminal force amplitude in lead V ₁	1.00	1.00–1.00	0.142			

Bold values indicate significance at p value < 0.05.

regression analysis; for CHADS₂ ≥ 4 HR 2.46 CI 95% 1.45–4.18, $p = 0.001$ and for CHA₂DS₂-VASc ≥ 5 HR 2.29 CI 95% 1.43–3.68, $p = 0.001$ (Fig. 2).

4. Discussion

In our study, we assessed the incidence of AF after first-ever ischemic stroke during a 10-year follow-up. Most studies of stroke outcome 10 years after stroke onset are limited by focusing on survival, [2] recurrent stroke [20] and quality of life [21]. Recently, the functional status of stroke survivors has been reported 10 years after stroke in patients enrolled in the LSR [4]. However, the literature data on AF incidence during long-term follow-up after stroke are sparse. In one study, the incidence of first-ever AF after ischemic or hemorrhagic stroke was assessed during 2 years and reported to be higher than the corresponding incidence calculated for the general population [8]. To our knowledge, there is a lack of detailed data on development of AF after first-ever ischemic stroke during long-term follow-up.

4.1. Detection of AF during follow-up

By the end of the 10-year follow-up, AF was detected in 15% of our entire, initially AF-free, study population (in 17% of stroke patients and 13% of control subjects), which corresponds to the reported AF incidence for an aging population: in one study, 18% of new AF cases were detected in people older than 85 years by the end of a 7-year follow-up [22] and another study reported AF of 17% in patients aged 65–74 years by the end of a 6-year follow-up [10].

AF screening studies performed with the use of implantable devices have generally reported much higher AF detection rates than studies based on ECG screening or national registries. The incidence of new AF during one year follow-up was shown to be 28% in patients after ischemic stroke or TIA [23] and 30% in patients with risk factors for ischemic stroke [24]. Continuous ECG recording in patients with implantable cardiac rhythm devices allowed detection of all episodes of AF, including asymptomatic ones. AF detected in our study is likely to be confined mostly to symptomatic AF episodes, which is supported by the higher frequency of ECGs recorded in patients who eventually developed AF. A number of asymptomatic AF episodes are likely to have been missed and therefore not available for analysis. In our study, more frequent ECG registration in patients with detected AF than in patients without AF may also reflect more frequent contact with health care providers due to higher prevalence of underlying cardiovascular disorders with manifested disease symptoms.

4.2. CHADS₂ and CHA₂DS₂-VASc scores as predictors of AF after ischemic stroke

CHADS₂ and CHA₂DS₂-VASc scores are routinely used in the assessment of stroke risk in patients with AF [16] and include known risk factors for AF development, such as age, hypertension, diabetes, myocardial infarction and cardiac failure [18,25]. The association of high cardiovascular risk profile measured by CHADS₂ and CHA₂DS₂-VASc scales with AF developing has been demonstrated in different cohorts [8–10] that is why we tested these scales as to assess their predictive value for new onset AF after first-ever ischemic stroke. In agreement with earlier reports, we found that the risk of new onset AF was related to the CHADS₂ and CHA₂DS₂-VASc scores, so that one in three stroke patients with CHADS₂ ≥ 4 or CHA₂DS₂-VASc ≥ 5 had new-onset AF documented during their post-stroke follow-up. Despite modest sensitivity and specificity, low scores, particularly CHA₂DS₂-VASc, had very high negative predictive value and might therefore be considered in assessment of AF risk after ischemic stroke and affect the choice of AF screening strategy.

Routinely used conventional 24-hour Holter monitoring has modest sensitivity for post-stroke AF detection [26,27]. Prolonged Holter

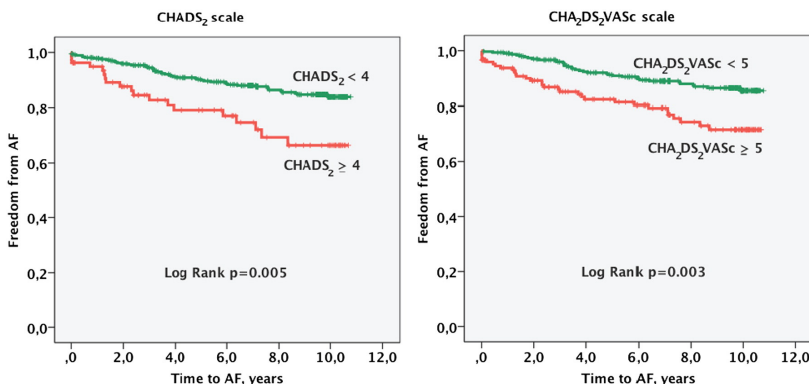


Fig. 2. Kaplan–Meier survival curve indicating new onset AF during 10-year follow-up according to different CHA₂DS and CHA₂DS₂-VASc scores in stroke patients without AF at their baseline stroke.

monitoring of up to 7 days increases post-stroke AF detection rates [5]. The highest AF detection rate after ischemic stroke has been reported in studies with ICM [7,28,29]. However, the usage of ICM-strategy in clinical practice is limited due to its invasiveness and high cost. It is very important to identify stroke patients who would derive the most clinical benefit from AF detection by prolonged ECG monitoring.

Conventional CHADS₂ and CHA₂DS₂-VASc appear to be useful instruments in this context, which is further supported by our findings.

4.3. ECG predictors of AF after ischemic stroke

There have been previous studies of the association of P wave duration and P terminal force in lead V₁ with the risk of AF. It has been reported that new-onset AF during long-term follow-up was associated with a prolonged P wave duration [30]. P wave duration is considered to be a non-invasive marker of atrial conduction and size. Its prolongation reflects atrial remodeling predisposing to occurrence of AF. In the Framingham Heart Study, the prolongation of P wave duration predicted the development of AF during long-term follow-up in an elderly community-based cohort [30]. In hypertensive patients, prolonged P wave duration was associated with AF incidence during a two-year follow-up [31].

However, in patients with congestive heart failure and severe cardiovascular risk factors, P wave duration was not predictive of new-onset AF [32]. In agreement with that study, we did not find an association of P wave duration with new onset AF after first-ever ischemic stroke during 10-year follow-up.

Although there are literature data indicating that P-terminal force of >0.04 mm/s as an electrocardiographic finding may predict new-onset AF [33], we could not reproduce those findings in our cohort. In our study, P-terminal force in lead V₁ was not predictive of new onset AF.

Surprisingly, we found the association of QRS duration with the development of AF after ischemic stroke. To our knowledge, there is a lack of literature data on the association of QRS characteristics with the risk of AF in ischemic stroke patients. However, it has been shown that in patients without structural heart diseases, an incomplete right bundle branch block was a marker for lone AF [34]. One possible explanation of that finding was that an incomplete right bundle branch block may be an early sign of fibrosis in a Purkinje system as a marker of the “physiological age” of the conduction system, including atrial tissue. In patients with left ventricular dysfunction, the association between QRS duration and the risk of AF has been found [14] in agreement with our findings for stroke patients with severe cardiovascular risk profile.

QRS duration may reflect myocardial fibrosis due to underlying cardiovascular disorders, which exists both in the ventricular and the atrium, and may be a substrate for AF development.

However, considering the level of significance of QRS association with new onset AF observed in our study (p value 0.049 in multivariate Cox regression model), it needs to be interpreted with caution, unless reproduced by others.

4.4. Comparison of stroke patients and control subjects

We could not detect a significant association between ischemic stroke and new-onset AF during the 10-year follow-up. The difference between the stroke group (17% of new AF cases) and the control group (13% of new AF cases) was not significant, possibly due to our small study sample size.

Although the literature data on this point are limited, higher incidence of first-ever AF after stroke has been reported in comparison with corresponding incidence calculated for the general population in the RIKS-Stroke study [8]. In that study, freedom from AF at baseline was assessed by a self-reported questionnaire and by linkage with the Swedish Patient Register, and the prevalence of AF at baseline was reported to be high (30%) [3]. However, some episodes of non-permanent AF prior to stroke may have been missed, so that the first-ever AF after stroke may not be the “true” first-ever AF. We reported an even higher pre-stroke AF prevalence (32%) by using ECG screening through electronic ECG archive and record linkage with national registers [15], which likely detected AF in patients who would otherwise be considered AF-free at inclusion in LSR, thus revealing a larger proportion of “true” new-onset AF after stroke. Our study with a 1:1 case-control design using the same comprehensive ECG screening for AF in both control subjects and stroke patients may be an explanation for the disparity between our findings and the findings of the RIKS-Stroke study, in which AF incidence was four times higher in stroke patients than the corresponding incidence of AF for the general population.

4.5. Study limitations

In our retrospective study, we did not use any pre-specified AF screening protocol. The number of ECGs during follow-up available for analysis was lower in subjects who had not detected new onset AF. This may lead to an underestimated “true” AF onset in patients with asymptomatic AF who had lesser need to contact health care providers. We have not been able to account for patients’ mobility between

different geographical regions, as our ECG search was limited to the ECG database that covers Southern Sweden's Skania region, and thus other ECG registrations possibly performed in other parts of Sweden were unavailable for review. In addition, we did not have data of prolonged ECG monitoring which now is widely used for AF detection and data of implantable devices. However, we obtained the information about AF by linkage with the Swedish Patient Register that contains up to 20 contributory diagnosis, which suggests that being found AF would be registered in the Swedish Patient Register, though we can obviously not claim completeness of AF information in that regard.

Finally, during 10 years follow-up after stroke a number of confounders might have arose especially in a small study population like the one we studied and our results should therefore be viewed in the light of this limitation.

5. Conclusion

A cardiovascular risk score assessed using conventional instruments such as CHADS₂ and CHA₂DS₂-VASc may identify ischemic stroke survivors who have an increased likelihood of developing newly diagnosed AF during follow-up and who may therefore become a target group for dedicated AF screening. Contrary to some earlier reports, our register-based study does not support an association between ischemic stroke and new-onset AF incidence during follow-up. QRS duration on admission ECG may be considered a potential predictor of new onset AF after ischemic stroke that warrants further evaluation.

Conflict of interests

None of the authors has any competing interests.

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Paper V

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 whether duration of AF episodes and its persistency affects long-term prognosis after ischemic stroke. We aimed to assess the impact of recurrent and permanent AF 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) which was followed-up for 10 years. 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 during FU was assessed via linkage with the Swedish Causes of Death Register.

Results: During FU 200 patients died. AF was an independent predictor of 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 as patients without AF (HR 0.71 95%CI 0.37-1.36, p=0.299), while the prognosis was worst for patients with permanent AF without OAC (HR 2.27 95%CI 1.40-3.66, p=0.001) and intermediate for patients with permanent AF on OAC (HR 1.61 95%CI 0.96-2.70, p=0.071).

Conclusion: All-cause mortality was independently associated with AF and was the worst 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.

Introduction

Atrial fibrillation (AF) is an established risk factor for ischemic stroke [1]. The majority of studies on AF in ischemic stroke patients are focused on detection of AF after ischemic stroke because detection of AF is crucial for initiation of secondary prevention therapy regardless of clinical types of AF. It has been shown that the incidence of ischemic stroke in patients with permanent AF and paroxysmal AF is similar [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. Though 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 outcome in first-ever ischemic stroke patients during a 10-year follow-up.

Materials and methods

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 detected using medical records, the data from regional electronic ECG database and by linkage with the Swedish National Patient Register as it was 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.

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 enrolment. Stroke severity was estimated using the National Institutes of Health Stroke Scale (NIHSS) [6]. For all study subjects, we evaluated cardiovascular risk profile at stroke using CHA₂DS₂-VASc score [1]. The index ischemic stroke was included when the score was calculated.

AF clinical types were categorized as permanent or recurrent [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 enrolment 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 judgment as documented in medical records, or when serial ECGs demonstrated arrhythmia without intervening sinus rhythm, including the ECG at admission [8].

Oral anticoagulation therapy

Novel 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 terminating and reasons of withdrawal for patients who were prescribed OAC.

End point and statistical methods

End point in this study was all-cause mortality. Vital status, dates of death, and primary and secondary diagnoses at 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 going back to 1961 and until 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 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 CHA₂DS₂-VASc score was analysed 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 severity of stroke. 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 which were associated with in-hospital mortality.

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).

Results

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.

Table 1.
Baseline clinical characteristics in first-ever ischemic stroke patients without atrial fibrillation, with permanent atrial fibrillation and with recurrent atrial fibrillation (AF).

Variable	No AF, n=227	Permanent AF, n=44	Recurrent AF, n=65	P value for permanent AF vs recurrent AF
Age, mean±std	71±12	83±7	78±9	0.003
Females, n (%)	92 (41)	18 (41)	26 (40)	1.000
Cardiac failure, n (%)	7 (3)	9 (21)	12 (19)	0.809
Hypertension, n (%)	130 (57)	28 (64)	37 (57)	0.533
Diabetes, n (%)	35 (15)	12 (27)	16 (25)	0.825
Vascular diseases, n (%)	95 (42)	16 (36)	31 (48)	0.324
CHA ₂ D ₂ S-VASc, mean±std	3.2±1.7	4.3±1.7	3.8±1.6	0.130
NIHSS scale, mean±std	5.3±6.2	8.8±9.0	9.0±9.6	0.885

During follow-up 200 (60%) of the 336 patients died with median time from stroke to death 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, $p = 0.005$).

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

At stroke admission 44 patients (40%) had permanent AF and 65 (60%) had recurrent AF (Table 1). 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.

Three hundred twenty two (96%) patients were discharged alive. Among 14 patients who died before discharge from hospital, 11 patients had AF: permanent in 4 and recurrent in 7 patients ($p = 1.000$), none of them was treated with OAC at admission. In multivariate logistic regression analysis after adjustment for age and clinical factors only severity of stroke 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 the highest impact on mortality was found for permanent AF (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 (Figure 1).

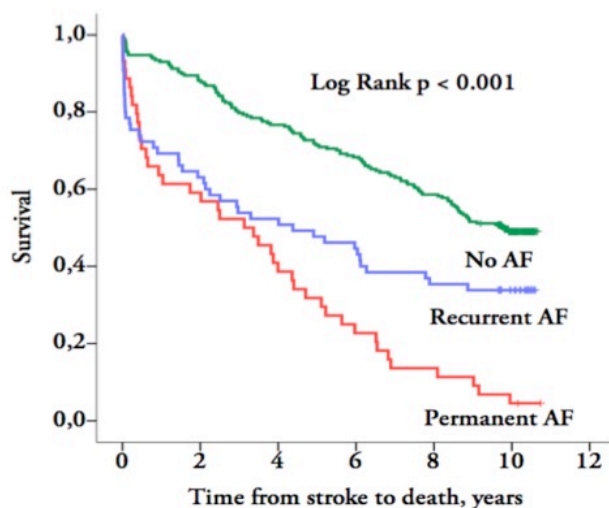


Figure 1
Kaplan-Meier survival curve indicating survival during 10-year follow-up in stroke patients without AF, with permanent AF and with recurrent AF.

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 them (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 0.4 years (IQ 0.2-2.3 years). In total, 44 stroke patients with AF (45%) received secondary prevention therapy during follow-up with median time being on OAC 4.8 years (IQ 0.9-8.8 years) for patients with permanent AF and 8.6 years (IQ 2.7-9.1 years) for patients with recurrent AF, $p=0.158$. Twenty-six patients (59%) continued receiving OAC till the end of FU

(n=18) or death (n=8), 6 patients ended OAC therapy due to complications, 5 – due to difficulties with warfarin dosage, 8 – due to unknown reasons.

At discharge, 4 patients with recurrent AF were not prescribed any antithrombotic medication. Twenty-two patients with permanent AF (55%) and 34 with recurrent AF (59%) received antiplatelet medications, either aspirin or clopidogrel, only one patient received combined therapy: aspirin plus clopidogrel. During follow-up the worst prognosis was observed for the 4 patients without antithrombotic therapy, the 46 patients receiving antiplatelet therapy had better prognosis compared to patients without therapy (HR 0.28 95% CI 0.13-0.58, p=0.001) and the best prognosis was observed for the 44 patients receiving warfarin compared to patients without therapy (HR 0.10 95% CI 0.05-0.23, p<0.001), Figure 2.

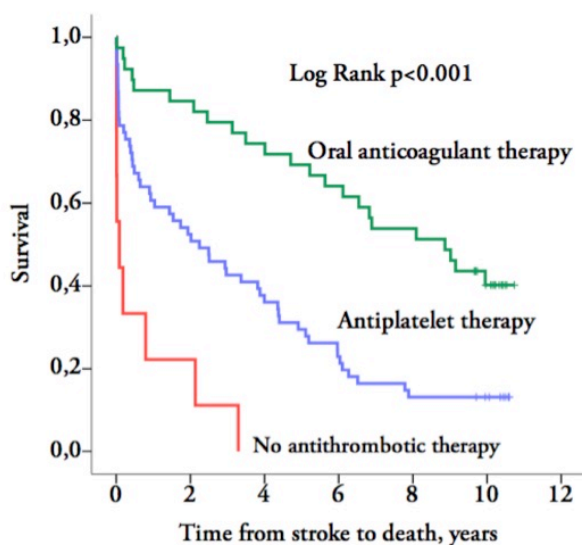


Figure 2
Kaplan-Meier survival curve indicating survival during 10-year follow-up according to discharge therapy in stroke patients with atrial fibrillation.

During the 10-year follow-up, patients with recurrent AF treated with OAC had similar survival as patients without AF history (HR 0.71 95%CI 0.37-1.36, p=0.299), while the prognosis was worst for patients with permanent AF without OAC (HR 2.27 95%CI 1.40-3.66, p=0.001) and intermediate for patients with permanent AF on OAC (HR 1.61 95% CI 0.96-2.70, p=0.071). In AF patients discharged without OAC, the type of AF did not appear to influence the long-term outcome (Table 2,

Figure 3). Patients receiving OAC with permanent AF had higher risk of mortality than patients receiving OAC with recurrent AF (adjusted HR 2.72 95% CI 1.04-4.98, p=0.04).

Table 2.

Cox regression analysis in patients with different clinical types of AF receiving or not receiving OAC therapy for prediction of 10-year all-cause mortality.

Variable	Univariate Cox regression analysis			After adjustment for independent predictors of mortality		
	HR *	95% CI	P value	HR	95%CI	P value
Recurrent AF + OAC	0.71	0.37-1.34	0.300	0.71	0.37-1.36	0.299
Permanent AF + OAC	2.34	1.41-3.90	0.001	1.61	0.96-2.70	0.071
Recurrent AF - OAC	3.74	2.53-5.52	<0.001	1.80	1.20-2.71	0.005
Permanent AF - OAC	6.09	3.87-9.60	<0.001	2.27	1.40-3.66	0.001

* -reference group – patients without AF

AF-atrial fibrillation

OAC – oral anticoagulant therapy

HR – hazard ratio

CI – confidence interval

Independent predictors of mortality – age, cardiac failure, severity of stroke.

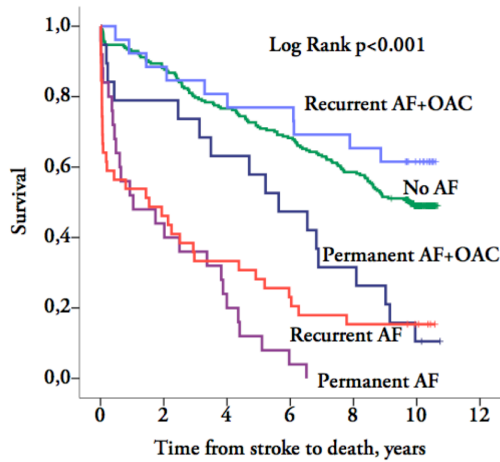


Figure 3
Kaplan-Meier survival curve indicating survival during 10-year follow-up according to different clinical types of AF and OAC therapy in stroke patients.

Discussion

To the best of our knowledge, this is the first study, in which the impact of OAC therapy on the long-term outcome was evaluated in relation to the clinical type of AF, i.e. permanent vs recurrent AF, in patients with ischemic stroke. The main findings are that patients with non-permanent AF treated with OAC after a first-ever ischemic stroke have a favorable outcome which is comparable to stroke patients without AF history. On the contrary, a worse prognosis was observed in stroke survivors with permanent AF. The lack of OAC after ischemic stroke was associated with poor long-term outcome regardless of the clinical form of the arrhythmia at the stroke event.

Predictors of all-cause mortality after first-ever ischemic stroke

The independent predictors of mortality after ischemic stroke were age, cardiac failure, stroke severity measured by NIHSS scale and AF. The strong association between AF and high all-cause mortality might be explained by that cardioembolic strokes have a more severe prognosis than non-cardioembolic strokes [13].

Impact of different clinical types of AF on outcome

Previously a more favorable outcome has been demonstrated for paroxysmal AF compared with chronic AF at discharge after ischemic stroke [3] and higher in-hospital mortality was found in stroke patients with permanent AF compared to stroke patients with paroxysmal AF [14]. In contrast to this we found a higher in-hospital mortality for patients with recurrent AF compared to patients with permanent AF. One possible explanation of this result is that, despite patients with paroxysmal AF are considered to be younger and healthier, patients with permanent AF more often received OAC therapy and therefore had better protection against cardioembolic stroke [2]. In our stroke population with AF the rate of OAC usage at stroke onset was generally low, but higher in patients with permanent AF, though the difference was not significant. However, this finding should be interpreted with caution due to the small number of patients died during hospital admission with ischemic stroke.

To the best of our knowledge, the literature data about the association between clinical types of AF and mortality in long-term follow-up after ischemic stroke are sparse. One study reported that patients with paroxysmal AF have lower mortality rates compared to patients with persistent and permanent AF during 10 years after ischemic stroke [4]. We found that stroke patients with AF have higher mortality during 10-year follow-up than stroke patients without AF and one of our main findings is that the prognosis was worse for patients with permanent AF compared to recurrent AF.

Though recent reports suggested that ischemic stroke incidence appears to be similar in paroxysmal and permanent AF [2], and that paroxysmal AF carries thromboembolic complications risk similar to permanent AF [15], some studies suggest that paroxysmal AF is associated with less severe strokes than permanent AF [3, 4, 16]. One possible explanation is that hemodynamic and hemostatic abnormalities, which are more profound in permanent AF than in paroxysmal AF, play an important role in the development of ischemic stroke [16]. It has been suggested that in patients with paroxysmal AF, abnormalities in hemostasis appears to be related to the duration of AF paroxysms [17]. More profound hemostatic disturbances and hemodynamic abnormalities in patients with permanent AF might be related to stroke severity due to thrombi formation with a relatively bigger size compared to patients with paroxysmal AF, causing infarcts of bigger volume and influencing the prognosis after stroke.

The severity of stroke might explain the worse prognosis for patients with permanent AF compared with patients with paroxysmal AF. However, in our study the severity

of stroke measured by NIHSS scale was similar in patients with recurrent AF and permanent AF. We found that patients with recurrent and permanent AF did not differ in regard to prevalence of diabetes mellitus, cardiac failure, hypertension, vascular diseases. This is in contrast to a study showing more favorable outcome 6 months after stroke for paroxysmal AF in which patients with permanent AF had higher proportion of cardiac failure and diabetes mellitus [16]. In the present study the only difference was observed for age where patients with permanent AF were older than patients with recurrent AF. In our multivariate Cox regression model, age was an independent predictor of mortality which is in agreement with earlier data [18]. However, even after adjustment for age in our study, AF remained an independent predictor of mortality with the highest impact on outcome observed for permanent AF.

Impact of OAC in different clinical types on outcome after ischemic stroke

According to current guidelines for the management of atrial fibrillation, all stroke survivors have CHA₂DS₂-VASc score of at least 2 and therefore have indication for OAC treatment [1]. Since our study population was recruited at the period of time when novel anticoagulants were yet not available, OAC therapy included only vitamin K antagonist – warfarin. Underuse of vitamin K antagonist is well known [19, 20]. In our study only 45% of stroke patients with AF received OAC therapy after discharge, while 51% were prescribed antiplatelet medications and 4% did not receive any antithrombotic treatment. Our data are in line with recently published data [21] showing that elderly patients with AF were prescribed vitamin K antagonist in 39% of cases, antiplatelet medications in 40%, and no antithrombotic therapy at all in 10%. In that study, during a mean follow-up of 1,5-years, all-cause mortality was lower in patients treated with OAC compared to patients treated without OAC, while the impact of antiplatelet therapy on prognosis was not analyzed separately. However, in the ACTIVE W substudy of stroke-free patient with AF, similar incident rates of ischemic stroke were reported for those receiving OAC and those receiving dual antiplatelet therapy [15]. In our study, AF patients discharged on one antiplatelet agent had better survival than AF patients without antithrombotic therapy, but worse survival than AF patients treated with OAC.

The benefit of OAC therapy in patients with AF and risk of thromboembolic complications is well established [1, 22] and our data are in line with this. However, little is known about the long-term prognosis in ischemic stroke patients and different clinical types of AF treated with OAC. A recently published subanalysis of the ROCKET-AF study [23], in which one third of patients had stroke in the past, reported that patients receiving anticoagulation with persistent AF have a higher risk of thromboembolic events and death compared to those with paroxysmal AF. This effect was seen in both in patients treated with warfarin and patients treated with

rivaroxaban. In agreement with that subanalysis, the stroke patients with recurrent AF in our study receiving OAC had better survival than patients with permanent AF receiving OAC. These data might have an important implication for the management of patients with AF; additional investigations are needed to determine the potential benefit of therapy aimed to prevent AF transformation from paroxysmal form into permanent AF.

Surprisingly, we found that stroke patients with recurrent AF on OAC therapy had the same prognosis as the stroke patients without AF, though AF had been proved to increase mortality after ischemic stroke [24]. One possible explanation of this finding is that patients with recurrent AF have not yet developed advanced cardiac remodeling and therefore have less profound hemostatic disturbances and hemodynamic abnormalities, which can be efficiently controlled by using OAC. Contrary, patients with permanent AF have cardiac remodeling leading to advanced hemostatic disturbances that cannot be fully controlled by using OAC. We observed a worse prognosis for patients without OAC therapy, regardless of clinical type of.

Study limitations

Several issues need to be kept in mind when interpreting our findings. In our study we evaluated only all-cause mortality and did not take into consideration the cause of death. The only end-point in our study was all-cause mortality, we did not assess recurrent ischemic strokes and bleeding complications. Also, during 10 years of follow-up after stroke a number of confounders might have appeared and might have influenced the prognosis, so our results should therefore be viewed in the light of this limitation.

Conclusion

The presence and the clinical type of AF significantly impacts long-term prognosis after first-ever ischemic stroke and should be considered in risk stratification. All-cause mortality was independently associated with the presence of AF and was worse for patients with permanent AF. Our findings further support the benefit of OAC therapy in patients with AF after first-ever ischemic stroke. Stroke patients with recurrent AF receiving OAC have the most favorable outcome which is similar to stroke patients without AF and significantly better than OAC-treated stroke patients with permanent AF.

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