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

DOCTORAL DISSERTATION
Due permission of the Faculty of Medicine, Lund University, Sweden
Dissertation will be defended at BMC Segerfalksalen, Wallenberg Neurocentrum
May 13, 2016 at 09.00

Faculty opponent
Professor Jens Cosedis Nielsen
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.

The thesis consists of a retrospective register-based study and a post hoc 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).

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).

Pre-stroke prevalence of AF appeared to be 32.4% and was associated with a high CHA$_2$DS$_2$-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 CHA$_2$DS$_2$-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 CHA$_2$DS$_2$-VASc score may be the target group for continuous AF screening and initiation of OAC therapy upon AF detection.

Key words: atrial fibrillation, ischemic stroke, CHADS$_2$, CHA$_2$DS$_2$-VASc, national patient register, ECG

Language: English

ISSN and key title 1652-8220
Lund University, Faculty of Medicine Doctoral Dissertation Series 2016:60

Recipient’s notes
Number of pages
Price
Security classification

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature
Date 01.04.2016
Atrial fibrillation in ischemic stroke: Prevalence, long-term outcomes and secondary prevention therapy

Maria Baturova
In memory of my mother
Contents

Papers ................................................................................................................................. 11
Abbreviations .................................................................................................................... 12
Introduction ......................................................................................................................... 13
Atrial fibrillation is a risk factor for ischemic stroke ......................................................... 13
Electrocardiographic screening for atrial fibrillation in ischemic stroke ......................... 14
Atrial fibrillation diagnosis in national patient registers .................................................... 14
Clinical factors, electrocardiographic and echocardiographic characteristics associated with atrial fibrillation .............................................................................. 15
  Clinical factors: CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores ................................................ 15
  Electrocardiographic characteristics: P-wave indices ................................................... 16
  Echocardiographic characteristics associated with AF: Left atrial volume index ... 17
Clinical types of atrial fibrillation in ischemic stroke: prevalence, impact on outcomes and oral anticoagulant therapy ................................................................. 18
Aims................................................................................................................................... 21
Material and methods ................................................................................................ ...... 23
  Study population ........................................................................................................... 23
    Lund Stroke Register .............................................................................................. 23
  Study cohort from the prospective Mayo Clinic study .............................................. 23
  Diagnosis and clinical types of atrial fibrillation ....................................................... 24
    Atrial fibrillation detection through electronic ECG archive ...................................... 24
    Atrial fibrillation detection by record linkage with national registers ................. 25
    Clinical types of atrial fibrillation: definitions ..................................................... 26
  Baseline clinical assessment ....................................................................................... 26
  ECG analysis ............................................................................................................... 26
  Echocardiography ....................................................................................................... 27
  Long-term outcomes ................................................................................................... 28
  Oral anticoagulant therapy ......................................................................................... 28
  Statistics ....................................................................................................................... 28
   Planned analyses ....................................................................................................... 29
     Study 1. Prevalence of AF and its clinical types prior to first-ever ischemic stroke 29
     Study 2. Validation of AF diagnosis in national registers ..................................... 29
     Study 3. ECG and ECHO predictors of paroxysmal AF detected after ischemic stroke ................................................................. 30
     Study 4. Predictors of new-onset AF during the 10 years following the first-ever ischemic stroke ................................................................. 30
Study 5. Impact of AF, its clinical types and secondary prevention therapy on long-term prognosis in patients with ischemic stroke ................................. 30

Results .................................................................................................................... 31
Baseline assessment of patients in the Lund Stroke Register cohort ..................... 31
Evidence of atrial fibrillation prior to ischemic stroke ........................................ 32
ECG validation of register-based diagnosis of atrial fibrillation ................................ 33
Clinical characteristics associated with atrial fibrillation in ischemic stroke patients 35
  Prevalent atrial fibrillation .............................................................................. 35
  Incident atrial fibrillation .............................................................................. 36
ECG characteristics associated with atrial fibrillation .......................................... 38
Echocardiographic parameters associated with atrial fibrillation .......................... 41
Clinical types of atrial fibrillation: prevalence at stroke onset and impact on long-term prognosis ................................................................. 41
Oral anticoagulant therapy at stroke admission and during 10-year follow-up ...... 43

Discussion ............................................................................................................ 47
Evidence of atrial fibrillation prior to ischemic stroke ......................................... 47
Validity of register-based atrial fibrillation diagnosis .......................................... 48
Atrial fibrillation detected using ambulatory ECG monitoring after ischemic stroke .............................................................................................................. 50
New onset atrial fibrillation during 10-year follow-up after first-ever ischemic stroke ........................................................................................................ 50
CHADS² and CHA²DS²-VASc scores associated with atrial fibrillation ................. 51
ECG characteristics associated with atrial fibrillation ......................................... 52
Echocardiographic parameters associated with atrial fibrillation ........................... 54
Clinical types of atrial fibrillation ....................................................................... 55
Oral anticoagulant therapy ................................................................................ 56

Conclusions ........................................................................................................ 59

Summary in Swedish ............................................................................................ 61

Acknowledgements ........................................................................................... 63
  Financial support .......................................................................................... 64

References ......................................................................................................... 65
Papers

1. Documentation of atrial fibrillation prior to first-ever ischemic stroke.
   Baturova MA, Lindgren A, Shubik YV, Olsson SB, Platonov PG.

2. Atrial fibrillation in patients with ischemic stroke in the Swedish national patient register: how much do we miss?
   Baturova MA, Lindgren A, Carlson J, Shubik YV, Olsson SB, Platonov PG.
   *Europace* 2014, 16(12): 1714-9

3. Electrocardiographic and Echocardiographic Predictors of paroxysmal Atrial Fibrillation detected after ischemic stroke.
   Baturova MA, Sheldon S, Carlson J, Brady PA, Lin G, Rabinstein AA, Friedman PA, Platonov PG.
   Submitted manuscript

   Baturova MA, Lindgren A, Carlson J, Shubik YV, Olsson SB, Platonov PG.
   *International Journal of Cardiology* 2015, 199: 248-252

5. Non-permanent atrial fibrillation and oral anticoagulant therapy are related to survival during 10 years after first-ever ischemic stroke
   Baturova MA, Lindgren A, Carlson J, Shubik YV, Olsson SB, Platonov PG.
   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 incertable 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: CHADS$_2$ and CHA$_2$DS$_2$-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 CHADS$_2$ 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).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 1. CHADS$_2$ score.
The CHA\textsubscript{2}DS\textsubscript{2}-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).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq 75$</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
<tr>
<td>Vascular diseases</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Female gender</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 2. CHA\textsubscript{2}DS\textsubscript{2}-VASc score.

CHADS\textsubscript{2} and the CHA\textsubscript{2}DS\textsubscript{2}-VASc scores identify patients at risk for developing stroke and thromboembolic events (6). The CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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 CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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 CHADS\textsubscript{2} 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 µV * 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.](image)

*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-ev er 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.
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 CHADS$_2$ and CHA$_2$DS$_2$-VASc scales (6). In Study I, the index ischemic stroke was not considered when CHADS$_2$ and CHA$_2$DS$_2$-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).
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 ± 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 CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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 CHA\textsubscript{2}DS\textsubscript{2}-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 CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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 (CHA\textsubscript{2}DS\textsubscript{2}-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.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Stroke group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All, n=336 AF, n=109</td>
<td>No AF, n=227</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>136(41) 44(40)</td>
<td>92(41)</td>
</tr>
<tr>
<td>Age, mean±std</td>
<td>74±12 80±8</td>
<td>71±12**</td>
</tr>
<tr>
<td>Cardiac failure, n (%)</td>
<td>8(8) 21(19)</td>
<td>7(3)**</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>195(58) 65(60)</td>
<td>130(57)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>63(19) 28(26)</td>
<td>35(15)**</td>
</tr>
<tr>
<td>TIA, n (%)</td>
<td>74(22) 25(23)</td>
<td>49(22)</td>
</tr>
<tr>
<td>Vascular diseases, n (%)</td>
<td>142(42) 47(43)</td>
<td>95(42)</td>
</tr>
<tr>
<td>CHA\textsubscript{2}DS\textsubscript{2}-VASC, mean±std</td>
<td>3.5±1.7 4.0±1.6</td>
<td>3.2±1.7**</td>
</tr>
<tr>
<td>NIHSS score, mean±std</td>
<td>6.5±7.5 8.9±9.3</td>
<td>5.3±6.2**</td>
</tr>
<tr>
<td>AF at baseline, n (%)</td>
<td>109(32) -</td>
<td>44(13) *</td>
</tr>
<tr>
<td>Permanent AF, n (%)</td>
<td>44(13) 44(40)</td>
<td>- 9(3) 9(20) ****</td>
</tr>
<tr>
<td>Recurrent AF, n (%)</td>
<td>65(19) 65(60)</td>
<td>- 35(10) 35(80)</td>
</tr>
</tbody>
</table>

* - 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).

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).
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 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).

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

<table>
<thead>
<tr>
<th>AF by SNPR</th>
<th>AF</th>
<th>No AF</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>152</td>
<td>36</td>
<td>81%</td>
</tr>
<tr>
<td>No AF</td>
<td>38</td>
<td>446</td>
<td>92%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>93%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th></th>
<th>All patients, n=672</th>
<th>Stroke group, n=336</th>
<th>Control group, n=336</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV, %</td>
<td>81</td>
<td>85</td>
<td>74</td>
<td>0.076</td>
</tr>
<tr>
<td>NPV, %</td>
<td>92</td>
<td>89</td>
<td>95</td>
<td>0.033</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>80</td>
<td>82</td>
<td>76</td>
<td>0.355</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>93</td>
<td>91</td>
<td>94</td>
<td>0.236</td>
</tr>
</tbody>
</table>

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 CHA\textsubscript{2}DS\textsubscript{2}-VASc scale (Figure 10).

![Figure 10](image)

The distribution of AF in stroke patients according to CHA\textsubscript{2}DS\textsubscript{2}-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 CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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.

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

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 ± 9 years vs 66 ± 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.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients without any AF, n=86</th>
<th>Patients with detected AF, n=24</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years ± std</td>
<td>66 ± 10</td>
<td>71 ± 9</td>
<td>0.033</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>55 (64)</td>
<td>15 (63)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>17 (20)</td>
<td>1 (4)</td>
<td>0.115</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>66 (76)</td>
<td>18 (75)</td>
<td>1.000</td>
</tr>
<tr>
<td>Vascular diseases, n (%)</td>
<td>17 (20)</td>
<td>4 (17)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cardiac failure, n (%)</td>
<td>4 (5)</td>
<td>2 (9)</td>
<td>0.604</td>
</tr>
<tr>
<td>CHADS2 score, mean ± std</td>
<td>3.2 ±0.9</td>
<td>3.2 ±0.9</td>
<td>0.996</td>
</tr>
<tr>
<td>CHA2DS2-VASc score, mean ± std</td>
<td>4.3 ±1.5</td>
<td>4.5 ±1.4</td>
<td>0.579</td>
</tr>
</tbody>
</table>

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).

![Kaplan-Meier survival curve indicating new-onset AF during 10-year follow-up in ischemic stroke patients and control subjects.](image)

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 CHADS\(_2\) and CHA\(_2\)DS\(_2\)-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 CHADS\(_2\) scale had sensitivity of 49%, specificity of 68% and negative predictive value of 86%. Cutoff 4.5 for the CHA\(_2\)DS\(_2\)-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 CHADS\(_2\) ≥ 4 HR 2.46 CI 95% 1.45-4.18, p=0.001 and for CHA\(_2\)DS\(_2\)-VASc ≥ 5 HR 2.29 CI 95% 1.43-3.68, p=0.001 (Figure 12).
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.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lund Stroke Register cohort</th>
<th>Mayo Clinic cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No AF, n=182</td>
<td>Patients with paroxysmal AF, n=52</td>
</tr>
<tr>
<td>P-wave duration, ms, mean±std</td>
<td>115 ± 17</td>
<td>116 ± 17</td>
</tr>
<tr>
<td>PR - interval, ms, mean±std</td>
<td>168 ± 29</td>
<td>189 ± 38</td>
</tr>
<tr>
<td>P-wave terminal force in lead V1, mm x ms, mean±std</td>
<td>22 ± 20</td>
<td>21 ± 21</td>
</tr>
<tr>
<td>QRS duration, ms, mean±std</td>
<td>99 ± 21</td>
<td>102 ± 20</td>
</tr>
<tr>
<td>Corrected QTc interval, ms, mean±std</td>
<td>437 ± 31</td>
<td>444 ± 33</td>
</tr>
<tr>
<td>IAB, n (%)</td>
<td>6 (3)</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

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)

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

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Cox regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>QTc interval</td>
<td>1.01</td>
</tr>
<tr>
<td>P wave duration</td>
<td>1.02</td>
</tr>
<tr>
<td><strong>QRS duration</strong></td>
<td><strong>1.02</strong></td>
</tr>
<tr>
<td>PQ interval</td>
<td>1.00</td>
</tr>
<tr>
<td>P terminal force amplitude in lead V1</td>
<td>1.00</td>
</tr>
</tbody>
</table>
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 $45 \pm 12$ ml/m$^2$, in stroke patients with detected short episodes of AF LAVI was $42 \pm 15$ ml/m$^2$, and in stroke patients without any AF LAVI was $32 \pm 10$ ml/m$^2$.

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/m$^2$ had an 84% negative predictive value for ruling out AF on ambulatory monitoring with sensitivity of 50% and specificity of 86%.

![Figure 13](image)

**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/m$^2$, 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).
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).
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.

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>After adjustment for independent predictors of mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR *</td>
<td>95% CI</td>
</tr>
<tr>
<td>Recurrent AF +OAC</td>
<td>0.71</td>
<td>0.37-1.34</td>
</tr>
<tr>
<td>Permanent AF +OAC</td>
<td>2.34</td>
<td>1.41-3.90</td>
</tr>
<tr>
<td>Recurrent AF -OAC</td>
<td>3.74</td>
<td>2.53-5.52</td>
</tr>
<tr>
<td>Permanent AF -OAC</td>
<td>6.09</td>
<td>3.87-9.60</td>
</tr>
</tbody>
</table>
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.

CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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 CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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 CHA\textsubscript{2}DS\textsubscript{2}-VASc score appears to be strongly linked to AF prevalence.

The risk of new-onset AF was related to CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores, such that one in three stroke patients with CHADS\textsubscript{2} ≥ 4 or CHA\textsubscript{2}DS\textsubscript{2}-VASc ≥ 5 had new-onset AF documented during their post-stroke 10-year follow-up. Despite modest sensitivity and specificity, low scores, particularly CHA\textsubscript{2}DS\textsubscript{2}-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 CHA\textsubscript{2}DS\textsubscript{2}-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-blockers 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 CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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/m\textsuperscript{2} 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/m\textsuperscript{2}, 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 CHA\textsubscript{2}DS\textsubscript{2}-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/m\textsuperscript{2} are less likely to develop paroxysmal AF on prolonged ambulatory ECG monitoring.
- High CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-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 CHA\textsubscript{2}DS\textsubscript{2}-VASc score may be the target group for continuous AF screening and initiation of OAC therapy upon AF detection.
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.

Syftet 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.


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 arytmia.

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 arytmiscreening.
Acknowledgements

Many people have contributed in various ways to the work that has resulted in this doctoral thesis. I would like to especially thank:

Professor Pyotr Platonov, my supervisor, for his splendid teaching, his willingness to share his experience and expertise, his patience and support, for always being positive, and for his great friendship. I have been tremendously fortunate to have a supervisor whose guidance was so gentle and so encouraging. I would like to thank Professor Platonov for opening the world of science to me, and for the exciting time during my PhD study.

Professor Arne Lindgren, my co-supervisor, for the opportunity to work with the data from the Lund Stroke Register, for his professional guidance, constructive criticism, and his help in expressing ideas and writing manuscripts.

Professor Yuri Shubik, my esteemed leader and teacher, who got me involved in atrial fibrillation research and made this work real. I thank Professor Shubik for his patience and his support during my study, his valuable advice on clinical arrhythmology, and for his kind input.

Professor S Bertil Olsson, whose contribution cannot be overestimated. I thank Professor Olsson for his professional guidance, his extremely valuable advice on how to express ideas, his encouraging support at all stages of my PhD study.

Dr. Jonas Carlson, for his invaluable assistance and his moral support. I am deeply grateful to Dr. Carlson for his willingness to help in sorting out the technical details of my work and his great help in solving software issues.

Dr. Paul Friedman, Dr. Alejandro Rabinstein and Dr. Seth Sheldon, thank you for the opportunity to work with the data from Mayo Clinic, for our productive collaboration, and your help in data processing and presentation of results.

Dr. Fredrik Holmqvist, my opponent at midway assessment, for his constructive criticism and valuable advice.

Monica Magnusson – thank you for your technical assistance during all the official stages of my PhD program.
Dr. Alexey Rivin, Dr. Alexey Saveliev, Dr. Mikhail Berman, Dr. Irina Aparina, Dr. Olga Veleslavova, Dr. Natalia Sokurenko, Dr. Marina Gordeeva, Dr. Mikhail Medvedev, Dr. Tatyana Kryatova, Anna Pronina and the entire staff of my clinical department for their moral support, and for making it possible for me to be away from the clinic once in a while during my PhD project.

Marina Kopjeva, my English teacher, for teaching me professional communication in English. Without her classes, this work would not be possible.

My family: my father Albert Galtsev, my husband Mikhail Baturov and my daughter Julia Baturova for their love, their support, for believing in what I was doing, and for helping in every way they could.

Financial support

This work was supported by a research scholarship from the Swedish Institute, by research grant from the Swedish Heart-Lung Foundation, by the Swedish National Health Service, by donation funds at the Skåne University Hospital, Lund, Sweden, and Region Skåne.
References


