

Catch **A**trial **F**ibrillation, Prevent Stroke

Detection of atrial fibrillation and other arrhythmias with short intermittent ECG

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*"I have tremor cordis on me: My heart dances;
But not for joy; not joy".*

The Winter's Tale, 1610, William Shakespeare

*To my family Olga, Zoya, Ilya, David, Kyrill, Vera, Efrosinia,
and my parents Hay and Renée*

TABLE OF CONTENTS

ABSTRACT	III
SUMMARY IN SWEDISH – SAMMANFATTNING PÅ SVENSKA	IV
ABBREVIATIONS AND ACRONYMS	VI
LIST OF ORIGINAL PAPERS	VIII
PREFACE	9
BACKGROUND	9
Atrial fibrillation – a short history	9
Definition of AF and atrial flutter	11
Types of AF	12
Mechanisms of AF	13
Epidemiology	13
AF, its causes and associations	16
AF and left atrial enlargement	17
AF and sleep apnea	17
AF, its outcomes	18
AF and stroke risk	19
Antithrombotic management in AF patients	22
Bleeding risk	23
Rate versus rhythm management	24
AF detection	24
Screening for AF	24
RATIONALE AND OBJECTIVES FOR THE THESIS	29
RESEARCH DESIGN AND METHODS	30
Material and methods	30
Statistical analysis	40
Ethical considerations	41
RESULTS	42
Paper I	43
Paper II	45
Paper III	47
Paper IV	49

DISCUSSION	53
Main findings	53
Methods and Results	53
General discussion	58
Expected importance and future perspectives	60
CONCLUSIONS	63
ACKNOWLEDGEMENTS	64
REFERENCES	66
APPENDICES	74
Appendix A. CRF data papers I-IV	74
Appendix B. Epworth Sleepiness Scale	78
ORIGINAL PAPERS	

ABSTRACT

Background: Atrial fibrillation (AF) is the most common arrhythmia in the adult population, affecting about 5% of the population over 65 years. Occurrence of AF is an independent risk factor for stroke, and together with other cardiovascular risk factors (CHADS₂/CHA₂DS₂-VASc), the stroke risk increases. Since AF is often paroxysmal and asymptomatic (silent) it may remain undiagnosed for a long time and many AF patients are not discovered before suffering a stroke.

Aims: To estimate the prevalence of previously undiagnosed AF in an out-of-hospital population with CHADS₂ ≥ 1, in patients with an enlarged left atrium (LA) and of total AF prevalence in sleep apnea (SA) patients, conditions that have been associated with AF. To compare the efficacy of short intermittent ECG with continuous 24h Holter ECG in detecting arrhythmias.

Methods: Patients without known AF recorded 10–30 second handheld ECG (Zenicor-EKG®) registrations during 14–28 days at home, both regular, asymptomatic registrations twice daily and when having cardiac symptoms. Recordings were transmitted through the in-built SIM card to an internet-based database. Patients with palpitations or dizziness/presyncope referred for 24h Holter ECG were asked to additionally record 30-second handheld ECG registrations during 28 days at home.

Results: In the out-of-hospital population with increased stroke risk, previously unknown AF was diagnosed in 3.8% of 928 patients. Comparing AF detection in patients with an enlarged LA versus normal LA showed that eleven of 299 patients had AF. Five of these had an enlarged LA (volume/BSA). No statistical difference in AF prevalence was found between patients with enlarged and normal LA, 3.3% and 3.2% respectively, ($p = 0.974$). AF occurred in 7.6% of 170 patients with sleep apnea, in 15% of patients with sleep apnea ≥ 60 years, and in 35% of patients with central sleep apnea. AF prevalence was also associated with severity of sleep apnea, male gender and diabetes. Comparing the efficacy of arrhythmia detection in 95 patients with palpitations or dizziness/presyncope with continuous 24h Holter and short intermittent ECG, 24h Holter found AF in two and AV-block II in one patient, resulting in 3.2% relevant arrhythmias detected. Short intermittent ECG diagnosed nine patients with AF, three with PSVT and one with AV-block II, in total 13.7% relevant arrhythmias. ($p = 0.0094$).

Conclusions: Screening in the out-of-hospital patient population (mean age 69.8 years) yielded almost 4% AF, making it seem worthwhile to screen older patients with increased stroke risk for AF with this method. Screening patients with LA enlargement (mean age 73.1 years) did not result in higher detection rates compared with the general out-of-hospital population. AF occurred in 7.6% of patients with sleep apnea, (mean age 57.6 years) and was associated with severity of sleep apnea, presence of central sleep apnea, male gender, age ≥ 60 years, and diabetes. Short intermittent ECG is more effective in detecting relevant arrhythmias than 24h Holter ECG in patients with palpitations or dizziness/presyncope.

SUMMARY IN SWEDISH – SAMMANFATTNING PÅ SVENSKA

Bakgrund: Förmaksflimmer (FF) är den vanligaste hjärtrytmrubbningen i den vuxna befolkningen. Med stigande ålder ökar förekomsten av FF. Fem procent av befolkningen över 65 år och mer än 10 % av befolkningen över 80 har FF. Förekomst av FF är en egen riskfaktor för stroke, och tillsammans med andra riskfaktorer (enligt CHADS₂ och CHA₂DS₂-VASc risk score): hjärtsvikt, hypertoni, ålder ≥65, ålder ≥75 år, diabetes och tidigare stroke, kvinnligt kön och kärlsjukdom ökar strokerisken. Eftersom FF ofta kommer attackvis och utan symptom kan det förbli odiagnostiserat under lång tid och många förmaksflimmerpatienter upptäcks inte förrän de får en stroke. FF upptäcks vanligtvis genom att man känner puls, vilo-EKG, 24-timmars Holter EKG eller event recorder EKG även om dessa metoder har en låg känslighet för att upptäcka attackvis och symptomfri FF.

Syfte: Studie I, III och IV: Att studera förekomsten av okänt FF med korta, intermittenta EKG registreringar under flera veckor i hemmet såväl i en öppenvårdspopulation med ökad stroke risk som bland patienter med en förstora vänster förmak och förekomsten av FF bland patienter med sömnapné, vilka anses vara associerade med en högre förekomst av förmaksflimmer och på så sätt bidra till ett underlag för eventuella framtida screeningprogram för FF. **Studie II:** Att jämföra effektiviteten av intermittent EKG-registrering med traditionell 24 timmars Holter EKG för att hitta hjärtrytmrubbningar hos patienter som remitterats för hjärklappning eller yrsel/svimmingskänsla.

Metod: I alla studier bad vi patienter, utan känt FF, registrera 10–30 sekunders tum-EKG (Zenikor-EKG®) hemma under 14–28 dagar, både regelbundna registreringar, morgon och kväll, och vid misstänkta symptom från hjärtat som kan tala för en hjärtrytmrubbning, såsom hjärtrusningar eller uttalat oregelbunden hjärtrytm. Registreringar överfördes av patienten med ett inbyggt SIM kort till en internetbaserad databas.

I **studie I** ombads 989 öppenvårdspatienter, utan känt FF och med minst en ytterligare riskfaktor för stroke göra 10-sekunders EKG registreringar under 28 dagar. I **studie II** ombads 108 patienter med symptom på hjärklappning eller yrsel/svimmingskänsla utan känt hjärtrytmrubbning, som remitterats för 24-timmars Holter-EKG, dessutom utföra 30-sekunders EKG registreringar under 28 dagar. Alla relevanta hjärtrytmrubbningar noterades. I **Studie III** ombads 300 patienter som hade gjort ultraljud av hjärtat, utan känt FF, ≥65 år, göra 30-sekunders EKG inspelningar under 28 dagar. Fynd av FF hos patienter med förstora och normalstort vänster förmak jämfördes. I **Studie IV** tillfrågades 251 patienter, som remitterats för sömnapnéutredning, om de hade känt FF. De patienterna utan känt FF ombads göra 30-sekunders EKG registreringar i 14 dagar.

Resultat: I **studie I** diagnostiserades 3,8 % nyupptäckt FF hos 928 patienter som fullföljde studien. I **Studie II** visade 24-timmars Holter undersökningen FF hos två och AV-block II hos en patient, totalt 3,2 % relevanta hjärtrytmrubbningar. Med korta, intermittenta EKG

upptäcktes nio patienter med FF, tre med PSVT och en med AV-block II, totalt 13,7 % relevanta hjärtrytmrubbningar. ($p = 0,0094$). I **Studie III** hittades elva nya paroxysmala FF patienter, fem med ett förstorat vänster förmak (volym/BSA). Ingen statistisk skillnad i FF förekomst syntes mellan patienter med förstorat och normalstort vänster förmak, 3,3 % (95 % CI 1,4–7,4) och 3,2 % (95 % CI 1,2–9,0) respektive, ($p = 0,974$). I **Studie IV** hittades sammanlagt 13 FF fall (7,6 %) bland 170 sömnapné patienter, ingen hittades bland icke-sömnapné patienter. Förekomsten av FF bland patienter med sömnapné över 60 års ålder var 15 % och bland patienter med central sömnapné 35 %. Förekomsten av FF ökade även för manligt kön och diabetes och med tilltagande allvarlighetsgrad av sömnapné.

Slutsatser: Studie I, III and IV: Screening i en öppenvårds population (medelålder 69,8 år) resulterade i upptäckt av nästan 4 % FF, vilket ger stöd för att screena äldre patienter, med ökad risk för stroke, för FF. Screening av patienter med ett förstorat vänster förmak (medelålder 73,1 år) resulterade inte i en större upptäckt av FF i jämförelse med den allmänna öppenvårdspopulationen. Undersökning av patienter remitterade för sömnapnéutredning (medelålder 57,6 år) resulterade i upptäckt av en FF prevalens av 7,6 % bland sömnapnépatienter och var associerad med allvarlighetsgrad av sömnapné, förekomst av central sömnapné, manligt kön, ålder över 60 år och diabetes. **Studie II:** Undersökning med korta, intermittenta EKG registreringar under ett flertal veckor är betydligt mer effektiv i att upptäcka relevanta hjärtrytmrubbningar än 24-timmars Holter EKG hos patienter med hjärtklappning eller yrsel/svimningskänsla.

ABBREVIATIONS AND ACRONYMS

ACE inhibitor	Angiotensin-Converting Enzyme inhibitors
AF	Atrial Fibrillation
AHI	Apnea-Hypopnea Index
ARB	Angiotensin Receptor Blocker
ASA	Acetyl Salicylic Acid
AV	Atrio-Ventricular
BMI	Body mass index
BSA	Body surface area
CAHI	Central Apnea-Hypopnea Index
CAST	Cardiac Arrhythmia Suppression Trial
CHADS ₂	Congestive heart disease, Hypertension, Age ≥65 years, Diabetes and earlier Stroke
CHA ₂ DS ₂ -VASc	Congestive heart disease, Hypertension, Age ≥75 years, Diabetes, earlier Stroke, Vascular disease, Age ≥65, female Sex
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSA	Central Sleep Apnea
CU	Cardiac Ultrasound
ECG	ElectroCardioGram
EF	Ejection Fraction
ESC	European Society of Cardiology
ESS	Epworth Sleepiness Scale
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly
ICD	International Classification of diseases
INR	International Normalized Ratio
ISD	Insertable Cardiac Device
LA	Left Atrium
LV	Left Ventricle
LVEF	Left Ventricle Ejection Fraction
NOAC	Novel Oral AntiCoagulants
OAHl	Obstructive Apnea-Hypopnea Index
OAC	Oral AntiCoagulation therapy
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PAD	Peripheral Artery Disease
PSVT	Paroxysmal SupraVentricular Tachycardia
QALY	Quality-Adjusted Life Year
QOL	Quality Of Life
RACE	Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation
RFA	Radiofrequency ablation
RR	Relative Risk
RR interval	R wave to R wave interval, the inverse of the heart rate

SA	Sinus Arrest
SA	Sleep Apnea
SBU	Statens Beredning för medicinsk Utvärdering (Swedish Council on Health Technology Assessment)
SCAF	SubClinical Atrial Fibrillation
SD	Standard Deviation
SPAF	Stroke Prevention in Atrial Fibrillation
SVES	SupraVentricular ExtraSystole
TE	Thrombo-Embolic
TEE	Trans-Esophageal Echocardiography
TLV	Tandvårds- och Läkemedelsförmåns Verket (Swedish Dental and Pharmaceutical Benefits Agency)
TTR	Time in Therapeutic Range
VKA	Vitamin K Antagonist
WCT	Wide Complex Tachycardia

LIST OF ORIGINAL PAPERS

- I. **Hendriks T**, Hörnsten R, Rosenqvist M, Sandström H.
Screening for atrial fibrillation with baseline and intermittent ECG recording in an out-of-hospital population.
BMC Cardiovasc Disord. 2013 Jun 10; 13:41.
- II. **Hendriks T**, Rosenqvist M, Wester P, Sandström H, Hörnsten R.
Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias.
BMC Cardiovasc Disord. 2014 Apr 1; 14:41.
- III. **Hendriks T**, Rosenqvist M, Wester P, Hörnsten R, Sandström H.
Screening for atrial fibrillation in patients with left atrial enlargement.
[Submitted]
- IV. **Hendriks T**, Sundqvist M, Hörnsten R, Sandström H, Sahlin C, Rohani M, Al-Khalili F, Blomberg A, Wester P, Rosenqvist M, Franklin K.
Atrial fibrillation in patients with sleep apnea.
[Manuscript]

PREFACE

Why this dissertation? A question I asked myself too.

What happened was that Mårten Rosenqvist in 2007 contacted Herbert Sandström at Family Medicine in Umeå to ask if he would be interested in participating in a primary care based study screening for atrial fibrillation (AF). The people in Västerbotten, known for being law-abiding and compliant, are a rewarding study population, more so than the obstinate people, in Stockholm's fragmented primary care world. Herbert was interested and as we at the time were working together at the Health Care Center of Lycksele, he asked me if I could consider becoming first author of this study. I agreed and after a pilot study we continued with the study published as paper I in this dissertation. During this time I was asked many times to enroll as a PhD student, but not until April 2011, when I was already involved in three other studies on AF detection, conceived by Mårten in cooperation with all other co-authors, did I make up my mind and registered as a PhD student.

BACKGROUND

Atrial fibrillation – a short history

Early history

Perhaps the earliest description of AF is in the Yellow Emperor's Classic of Internal Medicine (Huang Ti Nei Ching Su Wen). "When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender (smaller than feeble, but still perceptible, thin like a silk thread), then the impulse of life is small." The legendary emperor-physician is believed to have ruled China between 2697 and 2597 BC. ¹ Moses Maimonides described in some of his writings a totally irregular pulse that was most likely atrial fibrillation in circa 1187. ²

Early modern history

The poor prognosis associated with chaotic irregularity of the pulse was clearly acknowledged by most of the ancient physicians. In recorded history, William Harvey was probably the first, in 1628, to describe "fibrillation of the auricles" of the dying animal heart: "...but I noticed that after the heart proper, and even the right auricle were ceasing to beat and appeared on the point of death, an obscure movement undulation or palpitation had clearly continued in the right auricular blood itself for as long as the blood was perceptibly imbued with warmth and spirit". ³

The discovery of the therapeutic properties of digitalis leaf (*Digitalis purpurea*) in 1785 by William Withering brought some relief to patients with severe heart failure. Interestingly

Withering described a patient who had a weak and irregular pulse that became “more full and more regular” after five draughts containing Fol. Digitalis Purpurea oz iv. ⁴

Modern history

Marey and Chauveau passed metal sounds through the jugular veins of horses and interpreted their observations. In 1863 they were the first to publish pulse tracings of atrial fibrillation from humans with mitral valve stenosis. ⁵ Around 1900, a few clinical investigators, notably James Mackenzie in Scotland and Karel Wenckebach in Holland, studied cardiac arrhythmias with the use of arterial and venous pulse tracings. Mackenzie (1853–1925) noted the absence of the presystolic “a” wave seen in the jugular phlebogram during “pulsus irregularis perpetua”. He described his findings as the “most puzzling of all forms of irregularity of the heart, where the heart is never regular in its action, where seldom or never two beats of the same character follow one another”. ⁶

The main diagnostic breakthrough was the invention of the electrocardiograph by Willem Einthoven in 1900. Einthoven published an ECG tracing of atrial fibrillation (1906) without knowing its nature. He called it “pulsus inequalis et irregularis”. ⁷ Professor Einthoven had ongoing communication with Sir Thomas Lewis, ⁸ who made many important observations on atrial fibrillation in humans and performed a variety of experiments trying to understand the mechanism of atrial fibrillation. ⁹⁻¹¹ He defined it as “conspicuous and continuous oscillations of varying form and dimensions, and of auricular origin.” ¹¹ He further stated that atrial fibrillation affects the whole auricular surface with the excitation wave or its offshoots, and that it has a varying path of excitation.

In 1909, Rothenberger and Winterberger identified a direct connection between the “arrhythmia perpetua” and “fibrillation of the auricles”. Their paper from 1915 proposed that atrial fibrillation resulted from rapidly discharging spontaneously active ectopic foci. They postulated that the irregularity of the rhythm resulted from the interaction between the wave fronts produced by the focal generator and the variable refractory periods of the atrial tissue. ¹² In a study by Yater ¹³ in 1929, 145 patients underwent autopsy. The most common etiologies of these patients with atrial fibrillation were chronic endocarditis (19%), exophthalmic goiter (25%), adenomatous goiter (19%), and hypertension (8%). Yater further stated that no distinctive lesion for atrial fibrillation was found and that the lesions themselves were not considered of sufficient importance to explain the arrhythmia.

The exact mechanisms and importance of atrial fibrillation remained controversial until 1970 when Bootsma and coworkers concluded that the totally irregular response of the ventricles was due to the effect of “randomly spaced atrial impulses of random strength reaching the atrioventricular node from random directions”. ¹⁴ The epidemiological importance of atrial fibrillation as a precursor of cardiac and cerebrovascular death was investigated in detail in the Framingham study by Kannel and colleagues in 1982. Since then awareness of the

hazards of atrial fibrillation and the benefits of prophylaxis against thrombosis in preventing cerebral thromboembolism has increased. The recent explosion of literature on atrial fibrillation is impressive. A Medline search (2007) using atrial or auricular fibrillation as search words found 29,298 references from the time that Medline came into use. Most importantly, the last seven years of the search (2000–2007) counted for nearly half of all recorded publications.¹⁵ A new search on 24 February 2015 found 52,675 references.

Present

European Society of Cardiology (ESC) GUIDELINES for the management of Atrial Fibrillation 2010 and ESC FOCUSED UPDATE 2012^{16, 17}:

Definition of AF and atrial flutter

AF definition

AF is defined as a cardiac arrhythmia with the following characteristics¹⁶:

- (1) The surface ECG shows “absolutely” irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e. RR intervals that do not follow a repetitive pattern.
- (2) There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.
- (3) The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms.

Atrial flutter

Atrial flutter is a cardiac arrhythmia, characterized by reentry in the right (or left atrium), with the following features:

- 1) The surface ECG shows negatively directed saw-tooth atrial deflections (f waves) seen in leads II, III, and aVF, with positively directed deflections in lead V1.¹⁸
- 2) Atrial flutter is characterized by an organized atrial rhythm with a rate typically between 250 and 350 bpm.¹⁹

Atrial flutter has many clinical aspects similar to AF (underlying disease, predisposing factors, complications, medical management). Some patients have both atrial flutter and AF, and if left untreated, persistent atrial flutter can degenerate into chronic AF.¹⁹⁻²¹ In general, atrial flutter should be managed the same as AF. As both rhythms can lead to the formation of thrombus in the atria, individuals with atrial flutter and an increased stroke risk require anticoagulation. As both rhythms often have fast heart rates they may also require medication for rate and or rhythm control or electrical cardioversion. There are some specific considerations to treatment of atrial flutter. Atrial flutter is more sensitive to electrical cardioversion than AF, and usually requires a lower energy shock. Conversely, it is relatively resistant to chemical cardioversion, and can deteriorate into AF prior to spontaneous return to sinus rhythm. Because of the re-entrant nature of atrial flutter, it is

often possible to use radiofrequency ablation (RFA) to remove tissue from the re-entry circuit that causes atrial flutter.

Types of AF

Definitions

Paroxysmal AF is self-terminating, usually within 48 hours, but may continue up to seven days. The AF definition used in the ESC Guidelines 2010: “Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 seconds on a rhythm strip, should be considered as AF”.¹⁶ **Persistent AF** is present when an episode lasts longer than 7 days or requires termination by cardioversion. **Long-standing persistent AF** has lasted for ≥ 1 year when it is decided to adopt a rhythm control strategy. **Permanent AF** exists when the presence of AF is accepted by the patient and physician.

Silent AF

Silent AF or asymptomatic AF may manifest itself as an AF-related complication such as stroke or tachycardiomyopathy or may be diagnosed by an opportunistic ECG. It may have any of the temporal forms of AF described above. It has been estimated that only one in ten paroxysms of AF are symptomatic.²² It has also been estimated that one third of AF patients have asymptomatic AF²³, which was confirmed by data from a 2013 Halmstad study.²⁴ Silent AF has also been termed subclinical AF (SCAF) in the context of studies performing intensive ECG monitoring with devices such as implanted dual-chamber pacemakers and implantable cardioverter-defibrillators.^{25, 26}

Lone atrial fibrillation (LAF)

AF in the absence of clinical or echocardiographic findings of other cardiovascular disease (including hypertension), related pulmonary disease, or cardiac abnormalities such as enlargement of the left atrium, and age under 60 years.

Non-valvular AF

AF in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.

Secondary AF

Secondary AF occurs in the setting of a primary condition that may be the cause of the AF, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease

Natural time course of AF

AF progresses from short, rare episodes, to longer and more frequent paroxysmal attacks. Over a period of years, most patients will develop sustained forms of AF. Only a small

proportion of patients will remain in paroxysmal AF over several decades (2–3% of AF patients). “AF burden” can vary markedly over months or even years in individual patients.²⁷ Asymptomatic AF is common even in symptomatic patients, irrespective of whether the initial presentation was persistent or paroxysmal. This has important implications for (dis)continuation of therapies aimed at preventing AF-related complications.

Mechanisms of AF

Atrial factors

Any kind of structural heart disease may cause a progressive process of structural remodeling in both ventricles and atria, which may result in electrical dissociation and may facilitate the initiation and continuation of AF. After the onset of AF, changes of atrial properties occur, resulting in shortening of the atrial refractory time and deterioration of atrial contractile functions.¹⁶

Electrophysiological mechanisms

Focal activity from the pulmonary veins (PVs) may initiate and perpetuate atrial tachyarrhythmias.²⁸ These focuses are targets for ablation therapy.

According to the multiple wavelet theory, AF is continued by uninterrupted conduction of several independent wavelets spreading through the atrial musculature in a seemingly chaotic manor. Interaction of these wavelets sustains the arrhythmia.²⁹

Genetic factors

AF has a familial component, especially early-onset AF.³⁰ Numerous inherited cardiac syndromes, such as short and long QT syndrome and Brugada syndrome, have been associated with AF.³¹ A 2014 Swedish study showed that an AF-genetic risk score of twelve single nucleotide polymorphisms can identify 20% of individuals who are at two-fold increased risk for incident AF and at 23% increased risk of ischemic stroke.³²

Epidemiology

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. A recent Swedish study even suggesting 3%.³³ Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages.³⁴ The incidence of AF appears to be increasing already (13% during the past two decades).¹⁶ The prevalence of AF increases with age, from 0.5% at 40–50 years to 5–15% at 80 years.³⁴⁻³⁶ The lifetime risk of developing AF is 25% in those who have reached the age of 40.³⁷

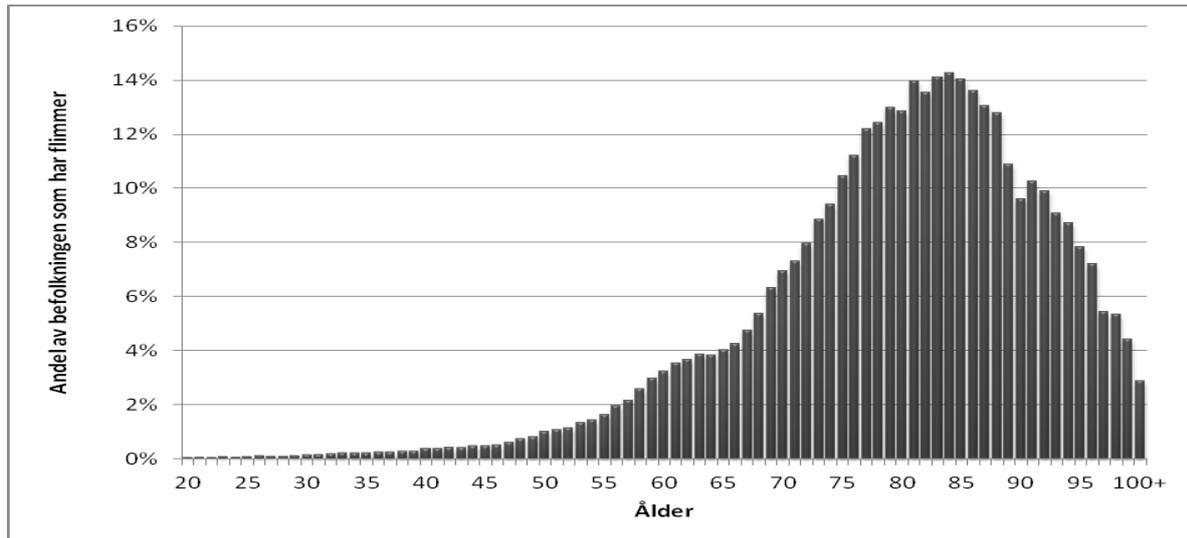


Figure 1. Prevalence (%) of AF in the Swedish population at different ages. National patient register, SBU report: Förmaksflimmer, förekomst och risk för stroke (AF, prevalence and risk for stroke), 2013.

AF may long remain undiagnosed (asymptomatic or silent AF)²⁷, and many patients with AF will never present to hospital.³⁸ Hence, the “true” prevalence of AF is probably higher than study data reveal.²⁷

AF and Gender

Men have a higher incidence of AF for all age groups compared to women (Figure 3). However, as the incidence of AF increases radically with age and because there are more women in the population ≥ 75 years, the absolute number of women and men with AF in this age group is equal.^{39,40} In general, women present at an age five years older than men, analogous to the later presentation of coronary artery disease in women. Women are more symptomatic than men, possibly because of faster heart rates and small body habitus.^{41,42} Compared with men, women are more likely to suffer a thromboembolic (TE) event or ischemic stroke when not taking Warfarin, but when they are prescribed Warfarin they have a comparable International Normalized Ratio (INR) control, are not more likely to suffer a major bleed and demonstrate a greater TE risk reduction.^{41,43}

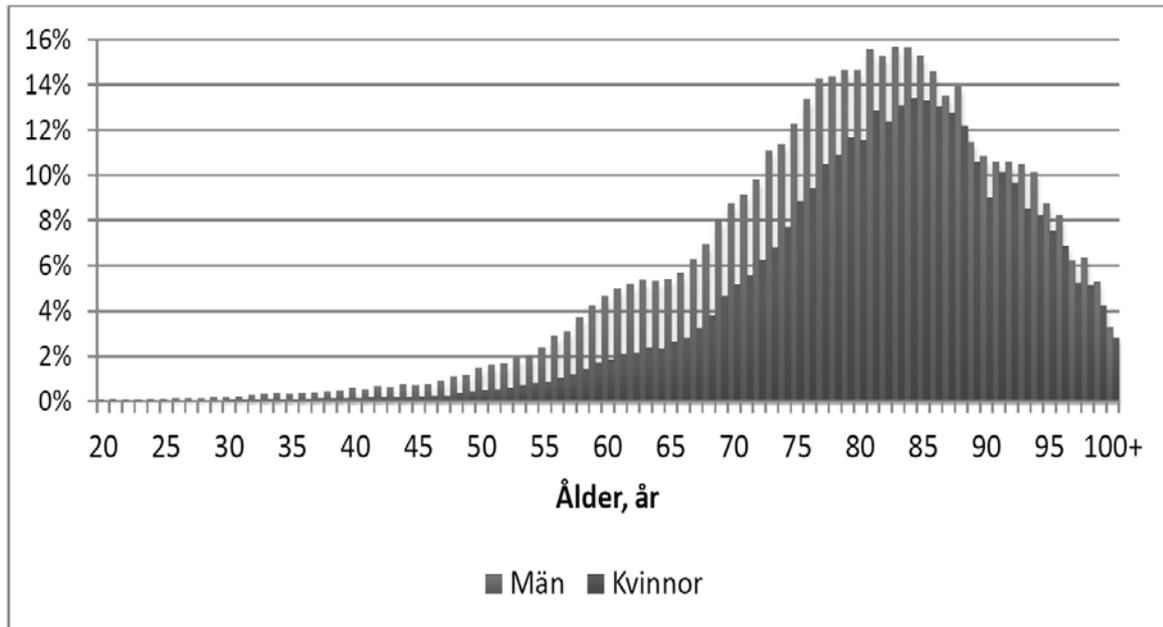


Figure 2. Prevalence (%) of AF (men in grey, women in black) in the Swedish population at different ages. National Patient Register, SBU report: Förmaksflimmer, förekomst och risk för stroke (AF, prevalence and risk for stroke), 2013.

AF and race

The prevalence and incidence of AF in non-Caucasian populations are less well studied. According to several studies, AF prevalence varies between races. According to one study, black patients, despite having many risk factors for AF, relative to white patients hospitalized for heart failure, had a lower prevalence of AF.⁴⁴ Another study on American male veterans showed white males having the highest AF burden even after adjustment for known risk factors. A higher prevalence was also seen in Native Americans and Pacific Islanders, a lower prevalence in Asians, Hispanics and blacks.⁴⁵

AF, its causes and associations

Causes and associations: cardiovascular and other conditions associated with AF

Conditions associated with AF are markers for global cardiovascular risk rather than simply causative factors.¹⁶

Ageing, being the most important risk factor for developing AF, possibly increases the risk of developing AF through age-dependent loss and isolation of atrial myocardium and associated conduction disturbances.¹⁶

Hypertension is a risk factor for incident AF and for AF-related complications such as stroke and systemic thromboembolism.¹⁶

Symptomatic heart failure [New York Heart Association (NYHA) classes II–IV] is found in 30% of AF patients,^{46,47} and AF is found in up to 30–40% of heart failure patients, depending on the underlying cause and severity of heart failure. Heart failure can be both a consequence of AF (e.g. tachycardiomyopathy or decompensation in acute onset AF) and a cause of the arrhythmia due to increased atrial pressure and volume overload, secondary valvular dysfunction, or chronic neurohumoral stimulation.¹⁶

Valvular heart diseases are found in about 30% of AF patients.^{46,47} AF caused by left atrial (LA) distension is an early manifestation of mitral stenosis and/or regurgitation. AF occurs in later stages of aortic valve disease. While “rheumatic AF” was a frequent finding in the past, it is now relatively rare in Europe.

Cardiomyopathies, including primary electrical cardiac diseases,⁴⁸ carry an increased risk of AF, especially in young patients. Relatively rare cardiomyopathies are found in 10% of AF patients.^{46,47} A small proportion of patients with “lone” AF carry known mutations for “electrical” cardiomyopathies.

Atrial septal defect is associated with AF in 10–15% of patients in older surveys. This association has important clinical implications for the antithrombotic management of patients with previous stroke or transient ischemic attack (TIA) and an atrial septal defect.¹⁶

Other **congenital heart defects** at risk of AF include patients with single ventricles, after Mustard operation for transposition of the great arteries, or after Fontan surgery.¹⁶

Coronary artery disease is present in ≥20% of the AF population.^{46,47} Whether uncomplicated coronary artery disease per se (atrial ischemia) predisposes to AF and how AF interacts with coronary perfusion⁴⁹ is uncertain.

Overt **thyroid dysfunction** can be the sole cause of AF and may predispose to AF-related complications. In recent surveys, hyperthyroidism or hypothyroidism was found to be relatively uncommon in AF populations,^{46,47} but subclinical thyroid dysfunction may contribute to AF.

Obesity is found in 25% of AF patients,⁴⁷ and the mean body mass index was 27.5 kg/m² in a large, German AF registry (equivalent to moderately obese).

Physical exercise and its influence on the onset and progression of AF are complex and variable and depend on age, comorbidities, intensity and duration of exercise. Several recent studies have demonstrated an increased AF risk with endurance exercise, especially in

middle-aged athletes.^{50,51} Other studies have also suggested that leisure time and vigorous exercise even at a non-competitive level increase AF risk in younger individuals.⁵⁰ In contrast, the Cardiovascular Health Study, a prospective study in adults >65 years of age, reported that light to moderate physical activities such as leisure-time activity and walking were associated to significantly lower risk of AF.⁵²

Alcohol consumption is positively associated with risk of AF. Even moderate consumption of alcohol, which lowers the risk of other cardiovascular diseases seems to slightly increase the risk of AF.⁵³

Diabetes mellitus requiring medical treatment is found in 20% of AF patients, and may contribute to atrial damage.¹⁶

Chronic obstructive pulmonary disease (COPD) is found in 10–15% of AF patients, and is possibly more a marker for cardiovascular risk in general than a specific predisposing factor for AF.¹⁶

Sleep apnea, especially in association with hypertension, diabetes mellitus, and structural heart disease, may be a pathophysiological factor for AF because of apnea-induced increases in atrial pressure and size, or autonomic changes.¹⁶

Chronic renal disease is present in 10–15% of AF patients. Renal failure may increase the risk of AF-related cardiovascular complications, although controlled data are sparse.¹⁶

AF and left atrial enlargement

The relation between AF and increased left atrial size has been long established, even before the widespread use of echocardiography.^{54,55} Echocardiographic studies have further confirmed and expanded on this finding, particularly in chronic AF.^{56,57} Data from large population-based studies have linked left atrial size to the development of AF.⁵⁸ In all likelihood, left atrial dilatation is associated with structural and functional atrial tissue alterations that facilitate the disturbed impulse propagation of AF.^{56,57} Evidence that increased left atrial size precedes the development of AF does not necessarily imply causality, though. It may simply be a marker for other factors that are causally related to the development of AF such as hypertension and ischemic heart disease. It is not known whether patients with left atrial enlargement on cardiac ultrasound (CU), without known AF, could be a suitable screening population for detection of AF.

AF and sleep apnea

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a common and under-diagnosed sleep-related breathing disorder. The prevalence of an apnea-hypopnea index of ≥ 5 in the North American population was found to be 24% in men and 9% in women.⁵⁹ OSA occurs when there are repetitive occlusions of the upper airway when obstructed by the tongue and soft palate. It is characterized by breathing effort during apnea. Obstructive sleep apneas are followed by

surges of sympathetic activity, an increase in blood pressure during apnea and a decrease in blood pressure and hypoxemia after apnea. ⁶⁰⁻⁶²

Patients with OSA run an increased risk of cardiovascular disease including stroke and early death. ⁶³⁻⁶⁵ Subjects with coronary artery disease have a 3-fold increased risk of stroke if they suffer from sleep apnea ⁶⁴, but the mechanism of sleep apnea related stroke is unknown. Sleep apnea is associated with incident atrial fibrillation and occurs in as much as 80% of patients with atrial fibrillation. ^{66, 67}

Central sleep apnea

No efforts to breath are made during central apneas. Central apneas occur most during Cheyne-Stokes respiration, a breathing pattern with repetitive increases and then decreases in tidal volume followed by a central apnea. Cheyne-Stokes respiration with central apneas occurs in 40-50% of patients with congestive heart failure and in some stroke patients. ^{68, 69} Central sleep apnea is generally considered the result of congestive heart failure or stroke ^{65, 69, 70}, because of hypocapnia, reduced cardiac output and enhanced sensitivity to carbon dioxide. ^{69, 71}

Atrial fibrillation is related to central sleep apnea in heart failure patients ⁷¹, and it is suggested that atrial fibrillation is a risk factor for central sleep apnea because it further deteriorates cardiac output.

Diagnosis

Overnight cardiorespiratory polygraphy records thoracic and abdominal respiratory movements, airflow from nasal cannulas, oxygen saturation, ECG and body position. Sleep apnea severity is characterized by the number of apneas and hypopneas per hour of sleep, the apnea-hypopnea index (AHI). Cut-off points of 5, 15 and 30 are used to indicate mild, moderate and severe sleep apnea. The same cut-off points are used for the obstructive apnea-hypopnea index (OAHI) and central apnea-hypopnea index (CAHI).

Sleep apnea and screening for AF

A recent review addresses the need of prospective studies screening actively for the presence of AF in patients with OSAS. Thereby giving the opportunity to detect AF early, treat with oral anticoagulation when appropriate and reduce the burden of stroke in this population. ⁷²

AF, its outcomes

Outcomes: cardiovascular events, except stroke caused by AF

AF is associated with increased rates of death, stroke and other thromboembolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity and left ventricular (LV) dysfunction. ¹⁶

Death rates are doubled by AF, independently of other predictors of mortality.^{27, 73} Only antithrombotic therapy has been shown to reduce deaths.⁷⁴

Hospitalizations, due to AF, account for one third of all admissions for cardiac arrhythmias. Acute coronary syndrome (ACS), aggravations of heart failure, thromboembolic complications and acute arrhythmia management are the main causes.¹⁶

Cognitive dysfunction, including vascular dementia, may be related to AF. Small observational studies suggest that asymptomatic embolic events may contribute to cognitive dysfunction in AF patients in the absence of an overt stroke.⁷⁵

Quality of Life (QOL) and **exercise capacity** are impaired in patients with AF. AF patients have a significantly poorer QOL compared with healthy controls, the general population or patients with coronary heart disease in sinus rhythm.⁷⁶

Left ventricular (LV) function is often impaired by the irregular, fast ventricular rate and by loss of atrial contractile function and increased end-diastolic LV filling pressure.¹⁶

Tachycardiomyopathy should be suspected when LV dysfunction is found in patients with a fast ventricular rate but no signs of structural heart disease. It is confirmed by normalization or improvement of LV function when good AF rate control or reversion to sinus rhythm is achieved.¹⁶

AF and stroke risk

AF confers a fivefold increased risk of stroke, and one in five of all strokes have been attributed to this arrhythmia.¹⁶ This earlier estimate of twenty percent seems an underestimation as of 24,132 Swedish patients with stroke 28.5% had AF at admission to hospital ([Riks-Stroke], unpublished information, 2007) and a 2013 registry study even concluded that AF had been present in 38% of ischemic events.⁷⁷ It has been estimated in earlier reviews that up to 8% of stroke patients without known AF have episodes of asymptomatic AF beyond that detected by physical examination and initial ECG during hospital admission for acute ischemic stroke.⁷⁸⁻⁸⁰ A 2015 review concludes that silent AF actually is the culprit in approximately 30 percent off cryptogenic stroke in patients with cardiac implanted electronic devices, which has important therapeutic implications, and concludes that oral anticoagulation should probably be prescribed when silent AF is detected.⁸¹

Ischemic strokes in association with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. In consequence, the risk of death from AF-related stroke is doubled and the cost of care is increased 1.5-fold.⁸²

Stroke risk in different types of AF

Current recommendations regarding anticoagulation treatment of AF to prevent patients from suffering a stroke are mainly based on evidence from studies dealing with persistent/permanent AF but suggest the same treatment for persistent/permanent and

paroxysmal AF in the presence of risk factors.^{16, 83, 84} A recent Swedish study shows that patients with paroxysmal AF have the same stroke incidence as patients with persistent/permanent AF.⁸⁵

Mechanism of stroke in AF

AF causes (cardio)embolic strokes. In this kind of stroke a blood clot travels from the left atrium and lodges in a brain artery, occluding it. The mechanism is as follows: when the left atrium does not produce effective, regular contractions as is the case in AF, contraction fails and blood is not completely squeezed from the left atrium into the left chamber. As a result blood remains in the atrium and may pool there. When blood has the opportunity to pool, it also has the opportunity to clot. If a blood clot forms in the left atrium, it can be pumped out of the heart to the brain, blocking off the blood supply to an artery in the brain, causing a stroke.

Risk assessment: CHADS₂ and CHA₂DS₂-VASc

CHADS₂

Occurrence of AF constitutes in itself an independent risk factor for stroke⁸⁶, and with concurrent other risk factors this risk is additionally increased. The identification of a number of risk factors for stroke in AF patients has led to the publication of various stroke risk schemes. Most have categorized stroke risk into “high”, “moderate”, and “low” risk strata. The simplest and most widely used risk assessment scheme when we started our first paper was the **CHADS₂** score. The CHADS₂ risk index (**C**ardiac failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke (doubled)) evolved from the Stroke Prevention in Atrial Fibrillation (SPAF) investigators’ criteria. It is based on a point system in which two points are assigned for a history of stroke or TIA and one point each is assigned for age ≥75 years, a history of hypertension, diabetes, or recent cardiac failure. The annual adjusted risk of ischemic stroke in AF is estimated to be 1.9–18.2% depending on the number of these risk factors (Table 1).⁸⁷ Risk factors are cumulative and the simultaneous presence of two or more risk points would justify a stroke risk that is high enough to require oral anticoagulation therapy (OAC) with Vitamin-K antagonists (VKA) such as Warfarin or any of the novel oral anticoagulants (NOAC). With AF in the presence of only one risk point, a choice between OAC and acetylsalicylic acid (ASA) has been recommended previously¹⁶, but the latest ESC focused update for management of AF¹⁷ does not recommend ASA anymore for stroke risk reduction in AF patients.

Table 1. CHADS₂ score and stroke rate.*

CHADS ₂ Score	adjusted stroke rate (% per year)	95% CI
0	1.9	1.2–3.0
1	2.8	2.0–3.8
2	4.0	3.1–5.1
3	5.9	4.6–7.3
4	8.5	6.3–11.1
5	12.5	8.2–17.5
6	18.2	10.5–27

* stroke rate assuming that aspirin was not taken ⁸⁷

CHA₂DS₂-VASc

A modification of this risk factor-based approach for patients with AF has resulted in a new risk score with the following acronym: **CHA₂DS₂-VASc** (Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female)). This scheme is based on a point system in which two points are assigned for a history of stroke, TIA or other thromboembolic event, or age ≥ 75 ; and one point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease, and female sex. ⁸⁸ This modification has been recommended in the latest European ESC guidelines for the management of AF. ¹⁶ In this modification prior stroke, TIA or thromboembolism, and older age (≥ 75 years) are “major” risk factors. “Clinically relevant non-major” risk factors are heart failure (especially moderate to severe systolic left ventricular dysfunction, defined arbitrarily as left ventricular ejection fraction (LVEF) $\leq 40\%$), hypertension, or diabetes. Other “clinically relevant non-major” risk factors (previously referred to as “less validated risk factors”) include female sex, age 65–74 years, and vascular disease (specifically myocardial infarction, complex aortic plaque, and peripheral artery disease (PAD), including prior revascularization, amputation due to PAD, or angiographic evidence of PAD). Even in this modification, risk factors are cumulative. The annual adjusted risk of ischemic stroke in AF is estimated to be 1.3–15.2% depending on numbers of these risk factors (Table 2). ^{88, 89} A 2012 Swedish registry study of more than 180 000 patients with AF, evaluating CHA₂DS₂-VASc, estimated stroke risk to range from 0.6–14.4%, for any TE event from 0.9–17.4%. ⁹⁰ According to the 2012 focused update of ESC guidelines, patients with AF who have stroke risk factor(s) ≥ 1 are recommended to receive effective stroke prevention therapy, which is essentially OAC with either well-controlled VKA therapy [INR 2–3, with a high percentage of time in the therapeutic range (TTR), for example, at least 70%] ⁹¹ or one of the NOACs. Patients < 65 years with lone AF (strictly defined irrespective of sex) do not need antithrombotic therapy. ¹⁷

Table 2. CHA₂DS₂VASc Score and rate of stroke or other thromboembolism.*

CHA ₂ DS ₂ -VASc Score	Adjusted rate of stroke or other thromboembolism (% per year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	12.5
9	15.2

*Stroke or other thromboembolism rate adjusted for warfarin use⁸⁹

Antithrombotic management in AF patients

OAC with vitamin K antagonists (VKA)

The increased risk of stroke in patients with AF can be reduced with OAC therapy. The vitamin K antagonist Warfarin has proved to be highly effective at reducing stroke risk with up to 64% in Relative Risk (RR) reduction, but is also associated with high monitoring costs and an increased risk of hemorrhage.⁹²

The level of anticoagulation is expressed as the International Normalized Ratio (INR), which is derived from the ratio between the actual prothrombin time and that of a standardized control serum. Based on achieving a balance between stroke risk with low INRs and an increasing bleeding risk with high INRs, an INR of 2–3 is the likely optimal range for prevention of stroke and systemic embolism in patients with non-valvular AF.^{93, 94}

NOAC

According to the focused ESC Update 2012, New Oral Anti-Coagulants (NOACs) offer better efficacy, safety, and convenience compared with OAC with VKAs. Thus, where an OAC is recommended, one of the NOACs—either a direct thrombin inhibitor (e.g. dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)—should be considered instead of adjusted-dose VKA (INR 2–3) for most patients with AF.^{17, 95, 96} There is insufficient evidence to recommend one NOAC over another, although some patient characteristics, drug compliance and tolerability, and cost may be important considerations in the choice of agent.¹⁷

In Sweden, the introduction of the NOACs has been relatively slow as a result of its well-functioning VKA treatment with high Time in Therapeutic Range (TTR). One study comparing TTR in the Auricula population with prospective randomized trials of warfarin treatment

showed a considerably higher TTR for the Auricula population. Auricula is the Swedish national quality registry for AF and anticoagulation. The same study also showed that complications were low, probably due to the organization of anticoagulation treatment in Sweden.⁹⁷

As the NOACs are not so new anymore, (e.g. dabigatran and rivaroxaban have been approved for prevention of venous thromboembolism in orthopedic patients in 2008 and for stroke prevention in AF patients in 2010/2011), their name has started to be replaced by DOACs (Direct OACs).

Antiplatelet agents

Antiplatelet agents such as ASA are also used to prevent stroke in AF but constitute a much less effective alternative.⁹² Direct comparison between the effects of Warfarin and ASA has shown that Warfarin is significantly more effective at preventing stroke.⁹⁸ The 2012 ESC focused update for management of AF¹⁷ does not recommend ASA anymore for stroke risk reduction in AF patients, because “the evidence for effective stroke prevention with ASA in AF is weak, with a potential for harm^{99,100}, as data indicate that the risk of major bleeding or intracranial hemorrhage (ICH) with aspirin is not significantly different to that of OAC, especially in the elderly.^{98,101} Given the availability of NOACs, the use of antiplatelet therapy (such as aspirin–clopidogrel combination therapy, or—less effectively—aspirin monotherapy) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC”.¹⁷

Bleeding risk

An evaluation of bleeding risk should be part of the patient assessment before starting anticoagulation.¹⁶ Using a “real-world” cohort of 3978 European subjects with AF from the EuroHeart Survey, a new simple bleeding risk score, **HAS-BLED** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR, **E**lderly (>65)¹⁰², **D**rugs/alcohol concomitantly), has been derived¹⁰³. A score of ≥ 3 indicates “high risk”, and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with Warfarin, NOAC, or ASA. The fact that hypertension, stroke and age over 65 years also are CHADS₂/CHA₂DS₂-VASc risk factors complicates this assessment. The conclusion of a large Swedish register study, however, was that in almost all patients with AF, the risk of ischemic stroke without anticoagulant treatment is higher than the risk of intracranial bleeding with anticoagulant treatment, and that more patients may benefit from anticoagulant treatment.¹⁰⁴

Rate versus rhythm management

Overwhelming evidence indicates that many patients with persistent AF can be managed effectively with a rate-control drug strategy and that there may be no benefit from a rhythm-control approach in these patients in terms of mortality, morbidity, or QOL.¹⁰⁵⁻¹⁰⁸ Moreover, the additional costs related to hospitalizations and drug expenses in patients being treated with rhythm control, and the relatively low rates of sinus rhythm maintenance, reinforce the need for careful patient selection. However, rate control may not be the best therapeutic choice for all AF patients, particularly those who are highly symptomatic. One thing that is very clear in these studies is the need for adequate anticoagulation, whether patients are on rate- or rhythm-control drugs. The RACE and AFFIRM studies both showed higher rates of thromboembolism in patients randomized to rhythm control, and the majority of these events occurred when patients had stopped taking warfarin or had a subtherapeutic INR.^{107, 108}

AF detection

An irregular pulse should always raise the suspicion of AF, but an ECG recording is required to diagnose AF. Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 s on a rhythm strip, should be considered as AF.¹⁶ AF in the general population is traditionally detected with pulse registration/palpation, 12-lead resting ECG, 24–48 hour Holter or event recorder ECG, but these methods have a relatively low sensitivity for detection of asymptomatic and paroxysmal AF.¹⁰⁹⁻¹¹²

Screening for AF

The 2012 ESC focused update states: “Diagnosing AF before the first complications occur is a recognized priority for the prevention of strokes.¹¹³ Recent data collected in patients with implanted devices,²⁵ and by Holter electrocardiograms (ECGs) in epidemiological studies,¹¹⁴ reinforce the assumption that even short episodes of “silent” AF confer an increased risk for stroke. We therefore recommend that, in patients aged 65 years or over, opportunistic screening for AF by pulse palpation, followed by recording of an ECG to verify diagnosis, should be considered for the early detection of AF.”^{109, 110} The European Heart Rhythm Association also stated in a 2011 position paper on palpitations that it is especially important to exclude AF as the underlying cause of symptoms in patients with palpitations of unknown origin.¹¹⁵

The sensitivity of pulse palpation, as recommended in the guidelines, and other traditional screening instruments, 12-lead resting ECG, 24–48 hour Holter or event recorder ECG, for

detecting relevant arrhythmias is comparatively low as symptoms in general are transitory, and the patients often are asymptomatic during the investigation.^{78, 110, 116, 117} Even when using (handheld or standard external loop) event recorders for a longer time period, episodes of an arrhythmia may be missed, as the correlation between symptoms and relevant arrhythmias is often not very strong. In atrial fibrillation (AF), for example, it is known that only one in ten paroxysms is symptomatic.²²

Patient-operated handheld devices for intermittent ECG recordings could potentially improve the diagnosis of transitory ECG changes and may give results comparable to standard external loop event recorders and may perform even better when combining symptomatic (event) and regular asymptomatic recordings^{118, 119}. The advantage of such handheld devices compared to standard external loop event recorders is that they are reasonably priced and easy to use, especially as no external electrodes are necessary. Recent studies show that handheld intermittent ECG recording with both regular and symptomatic registrations detects more episodes of silent AF in patients with known paroxysmal atrial fibrillation compared to 24-hour Holter ECG¹²⁰ and improves the detection of previously unknown asymptomatic paroxysmal atrial fibrillation (AF) in post-stroke patients.¹²¹

The handheld device

The ECG device used in our studies is Zenicor-EKG® (Figure 3), a handheld device that registers via both thumbs a bipolar extremity lead I-ECG during 10 to 30 seconds. After each registration, the recording is transmitted by the patient via an inbuilt mobile phone (SIM card) to a web-based central database. Symptomatic episodes can be marked with a button. In the database these symptomatic registrations are highlighted. The ability to give the correct diagnosis of AF compared to 12-lead ECG has shown a sensitivity of 96% and a specificity of 92%. A detailed technical description of the device, and its performance has been published in a study by Doliwa et al.¹²²



Figure 3. The handheld device

Other devices

Other methods and types of patient activated event recorders likewise show better results and cost effectiveness than 24 (and 48) hour Holter ECG.^{123, 124} A study from 2014 with another handheld device (Omron Heart scan 801®) detected more arrhythmias in a direct comparison with 24-hour Holter-ECG.¹²⁴ The authors describe detection of 2.6% supraventricular tachycardia and 1.4% atrioventricular nodal re-entry tachycardia, where 24-hour Holter did not find any cases at all. Disadvantages with this device are that recordings are saved on an SD card, it lacks an inbuilt SIM card and the device should be positioned against the thorax. Patch-based applications (e.g. Zio® Patch) with a possibility of continuous registration during a maximum of 14 days are another interesting alternative, where episodes during physical exertion, sleep and syncope are also recorded. In a study with 146 patients without known arrhythmia 61 arrhythmia events were discovered with 24 hour Holter and 96 with the patch ($p < 0.001$)¹²⁵. A disadvantage is that one cannot register for more than 14 days and one has to return the patch for analysis. Smartphone based applications could in the future also become alternatives for screening and monitoring paroxysmal arrhythmias. Examples are Alivecor and ECG check, which have been validated for event monitoring and AF screening¹²⁶. A disadvantage with all the above-mentioned alternatives compared with our method is that there is no infrastructure (data storage and analysis) for systematic use in Swedish healthcare at present.

Cost-effectiveness of screening with the handheld device

The Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV) has done a cost-effectiveness study (Kunskapsunderlag:

Hälsoekonomisk utvärdering gällande primärpreventiv screening av förmaksflimmer med tum-EKG, 2014, TLV)¹²⁷ based on unpublished data from the STROKESTOP study.^{128, 129} Preliminary data from the STROKESTOP study show a detection rate of 3% previously unknown AF. A pilot study for STROKESTOP in Halmstad, being done in parallel with the first manuscript in this thesis, detected 7.4% new AF cases when screening 75-year-old patients with CHADS₂ ≥2.²⁴ The purpose of the cost-effectiveness study was to determine whether primary preventive screening for AF with short intermittent recordings with handheld ECG is cost-effective for 75-year-old individuals. If fewer people contract a stroke it would give health gains and lower healthcare costs related to stroke. The report concluded that the advantages are great enough to warrant costs for screening and that the studied primary preventive screening is cost-effective based on our present scientific knowledge. Costs were estimated around SEK 39,000 SEK per added quality adjusted life year (QALY). A QALY costing less than SEK 500,000 SEK is usually deemed acceptable. In the United Kingdom e.g., the National Institute for Health and Clinical Excellence (NICE) is believed to have set a threshold 2005 at about £30,000 (around \$55,500) per additional QALY as the cut-off for what treatment costs are acceptable. Screening with handheld ECG does not reduce costs, but the total costs are low in relation to the health gained. (Hälsoekonomisk utvärdering gällande primärpreventiv screening av förmaksflimmer med tum-EKG, 2014, TLV).

Another study looking at secondary preventive screening in stroke patients comparing short intermittent ECG recordings and 24h Holter ECG with no-screening concluded that screening of silent AF with intermittent ECG recordings in patients with a recent ischemic stroke is a cost-effective use of health care resources, saving costs and lives and improving the quality of life.¹³⁰

Screening criteria by Wilson and Jungner (WHO) and the Swedish National Board of Health and Welfare (Socialstyrelsen)

Criteria for appraising the viability, effectiveness, and appropriateness of a screening program were first described by Wilson and Jungner for the World Health Organization (WHO) in 1968, but are still applicable today. All ten criteria are applicable for AF screening when participation and AF detection rates are high enough and if stroke is actually prevented. The Swedish National Board of Health and Welfare (Socialstyrelsen) had designed an adapted version with fifteen criteria. These criteria are also applicable to AF screening (Table 3).

Background

Table 3. The Wilson–Jungner criteria (WHO 1968) and Socialstyrelsen’s criteria for appraising the validity of an AF screening program (based on the STROKESTOP design).

WHO criteria	Socialstyrelsen	Applicability for AF screening
1) The condition sought should be an important health problem	1) The condition sought should be an important health problem	Yes , AF is a major cause of ischemic stroke and is associated with increased mortality, morbidity, and reduced quality of life
2) There should be an agreed policy on whom to treat as patients	2) There should be an agreed policy on whom to treat as patients ...	Yes , guideline documents are quite clear about which patients should be offered OAC
3) There should be an accepted treatment for the disease	2) ... and treatment should be acceptable for the intended population	Yes , all guidelines agree that OAC should be given to patients at high risk of AF-related stroke unless bleeding risk is very high
	3) Health gains should be greater than negative effects of a screening program	Yes , all guidelines agree that OAC should be given to patients at high risk of AF-related stroke unless bleeding risk is very high
4) Facilities for diagnosis and treatment should be available	4) Screening program resource requirements and feasibility should have been evaluated	Yes , facilities for diagnosis can be provided for. Treatment is part of the general health care system in Sweden
5) There should be a recognizable latent or early symptomatic stage	5) There should be a recognizable latent or early symptomatic stage 6) Treatment should give better results at an early stage than at clinical discovery	Yes , AF can be detected and treatment given before there is a stroke
6) There should be a suitable test or examination	7) There should be a suitable test or examination	Yes , permanent AF is easily detected with a single ECG recording. Intermittent AF requires prolonged ECG surveillance
7) The test should be acceptable to the population	8) The test and related further investigation should be acceptable to the population 9) Information about participation in the screening program should have been assessed 10) The screening program should be acceptable from an ethical viewpoint	Yes , ECG is non-invasive and without risk of bodily harm
8) The natural history of the condition, including development from latent to declared disease, should be adequately understood	11) The natural history of the condition should be adequately understood	Yes , the relationship between AF and stroke has been intensely studied and it is generally agreed that AF causes stroke
9) The cost of case finding (including diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole	12) Cost-effectiveness of a screening program should have been assessed and deemed reasonable	This will be tested by the STROKESTOP study. An assessment of preliminary data by TLV shows cost-effectiveness
10) Case finding should be a continuing process and not a “once and for all” project	13) Organizational aspects being relevant for a national screening program should have been clarified 14) There should be a plan for evaluation of effects of the screening program 15) A screening program should reduce mortality, morbidity and functional impairment related to the condition	Yes , if the main hypothesis of the STROKESTOP study is confirmed, it will provide an argument for extending the screening both in time, and geographically*. STROKESTOP plans to evaluate stroke incidence in the screened population as primary endpoint. Secondary endpoints: any thromboembolic event, intracranial bleeding, other major bleeding, first ever diagnosis of dementia, death from any cause, and a composite of these endpoints

* STROKESTOP will test the hypothesis that screening 75- and 76-year-old individuals for AF will reduce stroke incidence cost effectively i.e. that the cost of the screening is either (i) lower than the cost for the avoided strokes, or else (ii) that the cost per quality-adjusted life year gained by screening is low compared with other health care expenditures.

RATIONALE

What then is the answer to the question asked at the beginning of my preface: Why this thesis? After reading the 19-page introduction, I hope the answer has become somewhat clearer. Early detection of AF is of the utmost importance as it allows for timely introduction of therapies to protect patients from the consequences of the arrhythmia, especially oral anticoagulation therapy to prevent stroke. Defining suitable screening populations will contribute to early, effective AF detection.

OBJECTIVES

- I) To estimate the prevalence of undiagnosed AF among out-of-hospital patients, having at least one additional risk factor ($\text{CHADS}_2 \geq 1$) for stroke.
- II) To compare the efficacy of short intermittent ECG registrations with 24-hour Holter ECG, in detecting relevant arrhythmias in patients reporting symptoms of palpitations and dizziness/presyncope.
- III) To estimate the prevalence of undiagnosed AF in patients, referred for cardiac ultrasound, with an enlarged left atrium (LA) compared to those with a normal size LA.
- IV) To estimate the prevalence of previously diagnosed and undiagnosed AF in a population of patients referred for sleep apnea investigation. To evaluate which factors predict AF in patients referred for sleep apnea investigation.

RESEARCH DESIGN AND METHODS

Material and methods

Intervention

The handheld device and ECG screening method

In all four studies, we used Zenicor-EKG® (Figure 3), a handheld device, to detect previously unknown AF (**papers I and III**), both known and previously unknown AF (**IV**) or relevant arrhythmias including AF (**paper II**). The device records via both thumbs a bipolar extremity lead I-ECG during 10 to 30 seconds. Recordings are transmitted by the patient via an inbuilt mobile phone (SIM card) to a web-based central database. Symptomatic episodes can be marked with a button. In the database these symptomatic registrations are highlighted. Impaired cognitive function or other functional impairments that prevent the use of the device were used as an exclusion criterion in all studies. Patients made short ECG recordings (10 seconds (**paper I**) or 30 seconds (**papers II–IV**)) at home, twice a day and when having cardiac symptoms, during four weeks (**papers I–III**) or two weeks (**paper IV**). In **paper I**, patients with handheld ECG recordings with irregular series of SVES giving rise to AF suspicion were additionally asked to do a 24-hour Holter ECG. In **paper II** this method of short intermittent ECG recording was compared with 24-hour continuous Holter ECG in all patients. In **paper IV** patients had a 12-lead ECG at baseline.

ECG evaluation

ECG registrations were first evaluated by a study nurse. When in doubt the ECG was additionally checked by a physician, who had the possibility to contact a cardiologist. In **paper II** handheld ECG and Holter registrations were evaluated separately by two investigators who were blinded to the result of the other method. In cases of uncertainty, a consensus was reached by the two investigators and a cardiologist. Patients with detected AF or other relevant arrhythmias were referred for treatment in accordance with national guidelines.

Outcome measures: definitions of AF and other relevant arrhythmias

Paper I: AF on handheld ECG recordings was defined as irregular supraventricular extrasystoles in series with a duration of 10 seconds. Ambiguous recordings, showing repetitive irregular supraventricular extrasystoles (SVES) less than 10 seconds, were referred for an additional 24-hour Holter ECG. AF on Holter was defined by at least 10 seconds showing irregular rhythm without sinus P-waves.

Paper II: Significant arrhythmias were defined as: atrial fibrillation (AF) ≥ 30 seconds and AF defined as irregular heart rhythm without distinct sinus p-waves; paroxysmal supraventricular tachycardia (PSVT) ≥ 30 seconds, defined as regular rhythm, with supraventricular extrasystoles (SVES) in series, >120 beats/minute; atrioventricular (AV) block II–III; sinus arrest (SA) >2.5 seconds; wide complex tachycardia (WCT) with a QRS width of >120 ms and with a heart rate >100 beats/minute and at least 3 wide QRS complexes after each other.

Papers III and IV: We defined episodes of new AF on handheld ECG recordings as irregular supraventricular extrasystoles (SVES) in series with a duration of 30 seconds or two separate episodes of at least 10 seconds each. In **paper IV** all patients were questioned about earlier diagnosis of atrial fibrillation. Diagnoses were verified from patient records.



Figure 4. An example of AF and PSVT on handheld ECG from the ECG database (paper II).

An overview of material and methods for all four papers is presented in Table 4.

Table 4. Material and methods used in the four studies of this thesis

Paper	I	II	III	IV
Design	Prospective, cross-sectional	Prospective, comparative, cross-sectional	Prospective, comparative, cross-sectional	Prospective, cross-sectional
Research question	What is the prevalence of unknown AF in out-of-hospital patients with CHADS ₂ ≥1?	Are short intermittent ECG registrations during several weeks more effective than 24h Holter ECG in detecting arrhythmias in patients referred for symptoms of palpitations or dizziness, presyncope?	What is the prevalence of unknown AF in patients with an enlarged left atrium compared with patients with a normal size left atrium?	What is the prevalence of both known and unknown AF in sleep apnea patients? What factors predict AF in these patients?
Setting	Eight family practice centers and two out-patient clinics	Clinical Physiology, University Hospital	Clinical Physiology, University Hospital	Two hospital-based out-patient clinics
Subjects	989 consecutive out-of-hospital patients with CHADS ₂ ≥1, without known AF	108 consecutive patients referred for 24h Holter with palpitations or dizziness, presyncope, without known heart rhythm disorder	300 consecutive patients referred for cardiac ultrasound, ≥65 years, without known AF	251 consecutive patients, referred for cardiorespiratory polygraphy
Inclusion period	May 2007–June 2011	October 2010–May 2011	October 2011–April 2013	April 2012–November 2013
Interventions	10-second handheld ECG recordings, 28 days, twice daily and when having palpitations	30-second handheld ECG recordings, 28 days, twice daily and when having heart rhythm symptoms	30-second handheld ECG recordings, 28 days, twice daily and when having palpitations	Identification known AF. In those without known AF 12-lead ECG at baseline and 30-second handheld ECG recordings, 14 days, twice daily and when having palpitations
Main outcome measures	Episodes of AF with a duration of 10 seconds	Episodes of AF (30 seconds), PSVT (30 seconds), AV block II–III, SA (2.5 seconds) or WCT	Episodes of AF in at least one registration of 30 seconds or in two registrations ≥10 seconds	Known AF or episodes of AF in patients without previously known AF on 12-lead ECG or handheld ECG, with a duration of 30 seconds or in two registrations ≥10 seconds

Case report form

Demographic data and results for all four papers were collected in a Case Report Form (CRF) and stored at a web-based central database. For CRF data of **papers I–IV** see Appendix A.

Holter

In **papers I and II** Holter recordings were performed using a standard recording unit (Breamer DL700, Breamer Inc. Burnsville, MN, USA). Holter recordings were automatically analyzed by a PC-based Holter system (Aspect Holter System, GE Healthcare, Stockholm, Sweden).

Cardiac Ultrasound

In **paper III** both Vivid 7, GE Medical systems (Horten, Norway) with a phased-array transducer (1.5–4.0 MHz) and Acuson Sequoia 512 echocardiograph (Acuson Corporation, Mountain View, CA, USA) were used for cardiac ultrasound. From start, data on LA diameter were measured with a cut-off value of 40 mm for enlarged LA without taking body surface area (BSA) into consideration. Later these values were converted to index diameter (cm/m²) and index volume (ml/m²) was also measured. All measurements were end-systolic, biplane. In addition, EF and LA strain were measured.

Table 5. Reference values for LA enlargement (LA size, index).

	Normal	Mild	Moderate	Severe
LA diameter (cm/m ²)	1.5–2.3	2.4–2.6	2.7–2.9	≥3
LA volume (ml/m ²)	16–28	29–33	34–39	≥40

BNP analysis

In **paper III** for BNP analysis the Alere Triage® BNP Test, a rapid, point-of-care fluorescence immunoassay was used. The test is used to measure B-type natriuretic peptide (BNP) in EDTA anticoagulated whole blood or plasma specimens.

Table 6. Reference values Triage BNP.

	normal	mildly elevated	elevated
BNP (pg/ml)	0–99	100–499	≥500

Cardiorespiratory polygraphy

In **paper IV**, we used Embletta X10 system (Embla systems, 1 Hines Road, Suite 202, Kanata, ON K2K 3C7, Canada) for cardiorespiratory polygraphy measurements at home. Nonin Oximeter, XPOD, Embletta (Nonin Medical, Inc, 13700 1st Avenue North, Plymouth, Minnesota, 55441-5443 USA) was used for pulse oximetry. Sleep apnea severity was characterized by the number of apneas and hypopneas per hour of sleep, the apnea-hypopnea index (AHI). Obstructive apneas were defined as a cessation of airflow for at least

10 seconds. Obstructive hypopneas were defined as a 50% reduction in airflow for at least 10 seconds in combination with an oxygen desaturation of 3% or more. In central apneas, there are no efforts to breathe, no thoraco-abdominal movements and no airflow for at least 10 seconds. Cut-off points of AHI 5, AHI 15 and AHI 30 were used to indicate mild, moderate and severe sleep apnea.¹³¹ The same cut-off points were used for the obstructive apnea-hypopnea index (OAHI) and central apnea-hypopnea index (CAHI). The Oxygen Desaturation Index (ODI) is the number of times per hour of sleep that the blood's oxygen level drops by 3% or more from baseline.

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a subjective measure of a patient's sleepiness.¹³² The test is a list of eight situations in which patients rate their tendency to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing. When finishing the test, added values result in a total score of 0 to 24.

0–7: It is unlikely that the patient is abnormally sleepy.

8–9: The patient has an average amount of daytime sleepiness.

10–15: The patient may be excessively sleepy depending on the situation.

16–24: The patient is excessively sleepy and should consider seeking medical attention.

For the ESS questionnaire, see appendix B.

Design, study populations and settings

All four studies were observational studies. They were prospective and cross-sectional. In each paper, a different population was studied. Patients were not included in more than one of the studies.

Paper I: 989 patients from eight family practice centers (six in Västerbotten County and two in Stockholm County) and two hospital-based out-patient clinics (both in Stockholm County) in Sweden, having one or more risk factors associated with stroke (CHADS₂ ≥1), without known AF, were identified from physicians' and nurses' surgery lists and included consecutively.

Inclusion criteria: one or more risk factors associated with stroke (CHADS₂ ≥1). *Exclusion criteria:* known AF, impaired cognitive function or other functional impairments that prevent the use of the handheld device.

The detection rate of AF, mean age and mean CHADS₂ were comparable at all ten centers and this together with the size of the study population, consecutive inclusion, a very high participation rate and low dropout increases the likeliness of representativeness of the study population in comparison with out-of-hospital patients with comparable age and comorbidities in general.

Paper II: 108 consecutive patients with symptoms of ambiguous palpitations or dizziness/presyncope, referred to the Department of Clinical Physiology, Norrland University Hospital, Umeå, for 24-hour Holter ECG, were included.

Palpitations were defined as a sensation in which a person is aware of an irregular, hard, or rapid heartbeat. Dizziness/presyncope was defined as a sensation in which a person experiences light-headedness, unsteadiness or near fainting. *Exclusion criteria* were: known arrhythmia, based on previous history or 12-lead ECG performed at the time of referral; referral for syncope, defined as temporary loss of consciousness; or comorbidity with cognitive or other functional impairments impeding the use of the handheld device. Consecutive inclusion and the fact that the Department of Clinical Physiology is the only center in Västerbotten County for this type of service increases the likeliness of representativeness of the study population in comparison with patients contacting health care with complaints that might be caused by an arrhythmia (palpitations or dizziness/near-syncope) in general.

Paper III: 299 patients, ≥ 65 years ($\text{CHA}_2\text{DS}_2\text{-VASc}$ of ≥ 1), without known AF, referred to the Department of Clinical Physiology, Norrland University Hospital (NUS), Umeå, for Cardiac Ultrasound (CU), were included consecutively. Exclusion criteria were: known AF and cognitive or other functional impairments impeding the use of the handheld device. Consecutive inclusion and the fact that the Department of Clinical Physiology is the only center in Västerbotten County for this type of service increases the likeliness of representativeness of the study population in comparison with patients with an enlarged left atrium in general.

In addition LA volume and diameter were investigated in a *comparative group* of 29 patients from the same catchment area with known persistent AF for more than ten months, identified from the Swedish National Discharge Register using code I489 for AF, ICD-10 (International Classification of Diseases, 10th revision), between 1 January 2012 and 30 April 2014. These patients were matched for age with the original study population and matched for sex ratio with the Swedish AF population at age 71.

Paper IV: 251 patients from two hospital-based out-patient clinics (Department of Respiratory Medicine, Umeå University Hospital, Umeå, Sweden (n=152) and Stockholm Heart Center, Stockholm, Sweden (n=99)), referred for cardiorespiratory polygraphy, were randomly assigned for inclusion at days when a study nurse and equipment for atrial fibrillation detection was present. Exclusion criteria: impaired cognitive function or other functional impairments that prevent the use of the handheld ECG device.

Study Flowcharts

Study flowcharts from **papers I–IV** are presented below.

Paper I: Screening for atrial fibrillation with baseline and intermittent ECG recording in an out-of-hospital population

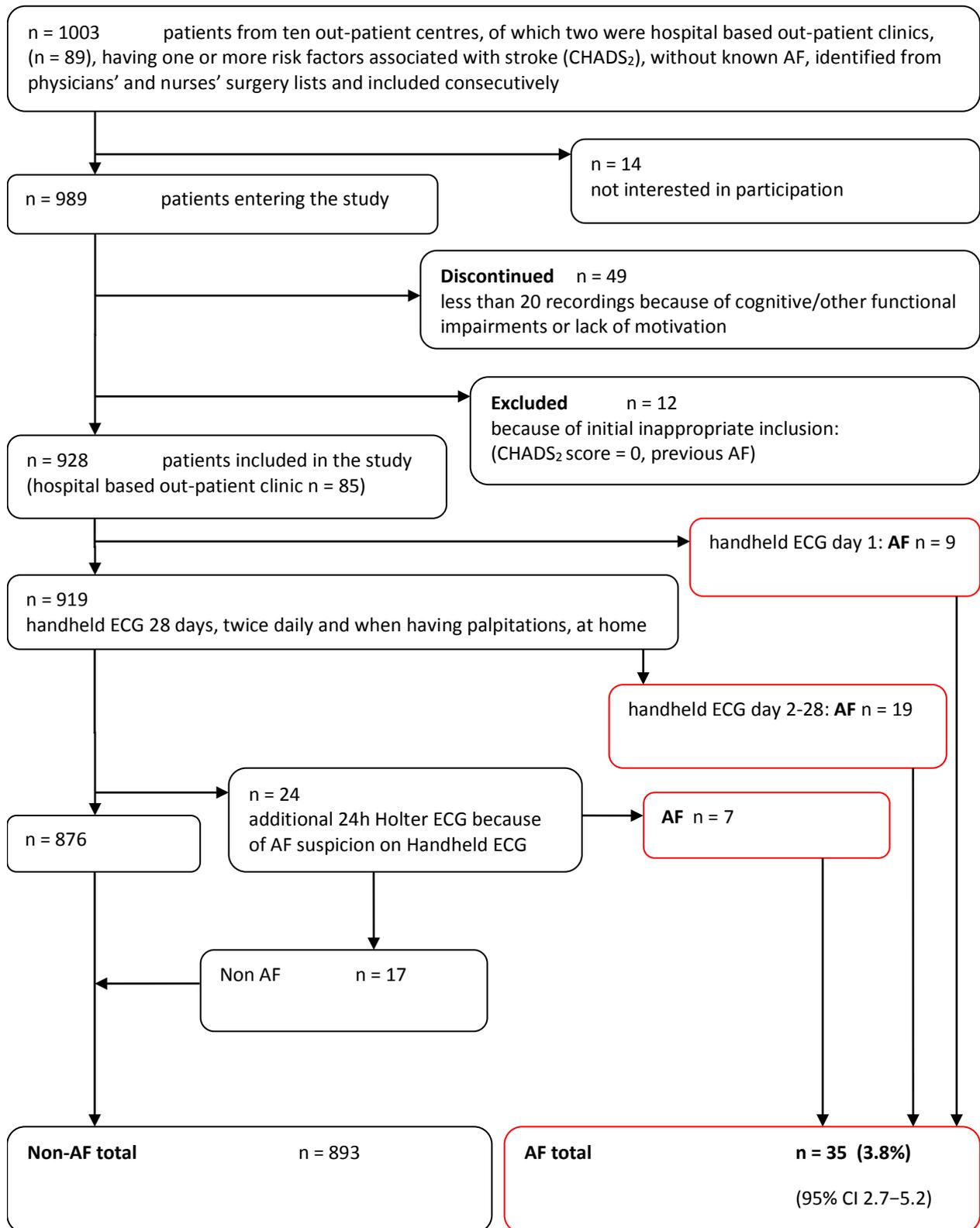


Figure 5. Flowchart Paper I.

Paper II: Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias

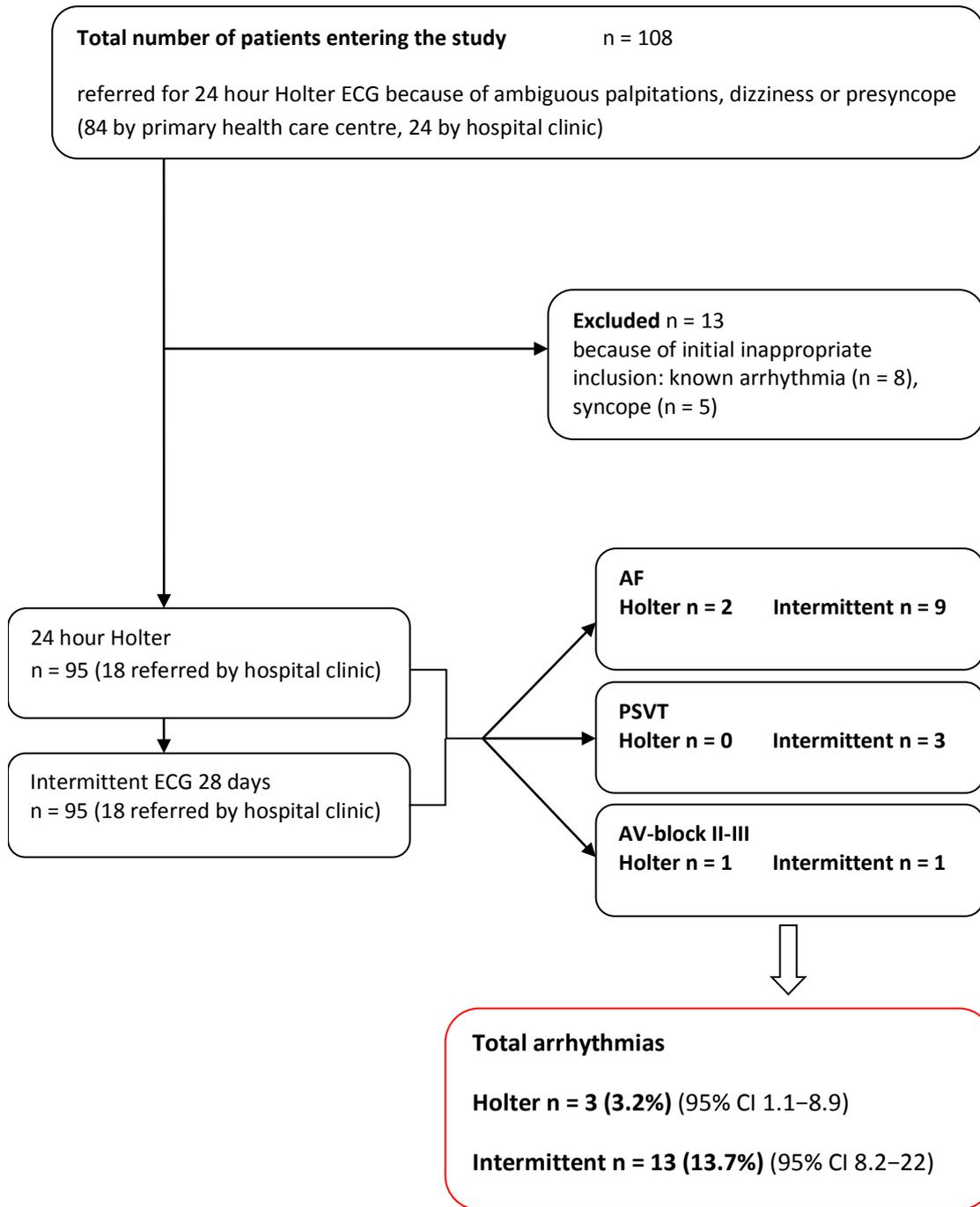


Figure 6. Flowchart Paper II.

Paper III: Screening for atrial fibrillation in patients with left atrial enlargement

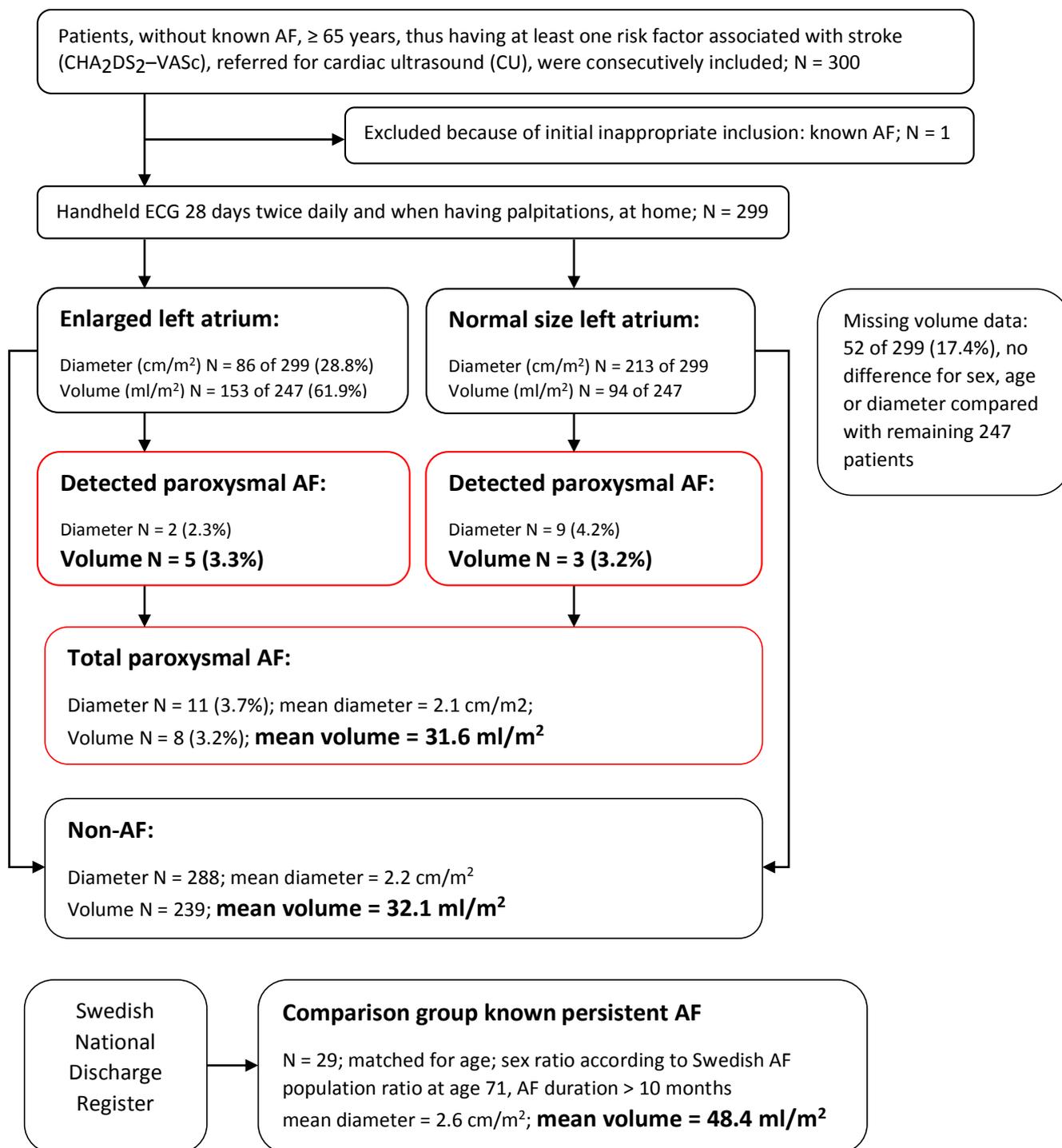


Figure 7. Flowchart paper III.

Paper IV: Atrial fibrillation in patients with sleep apnea

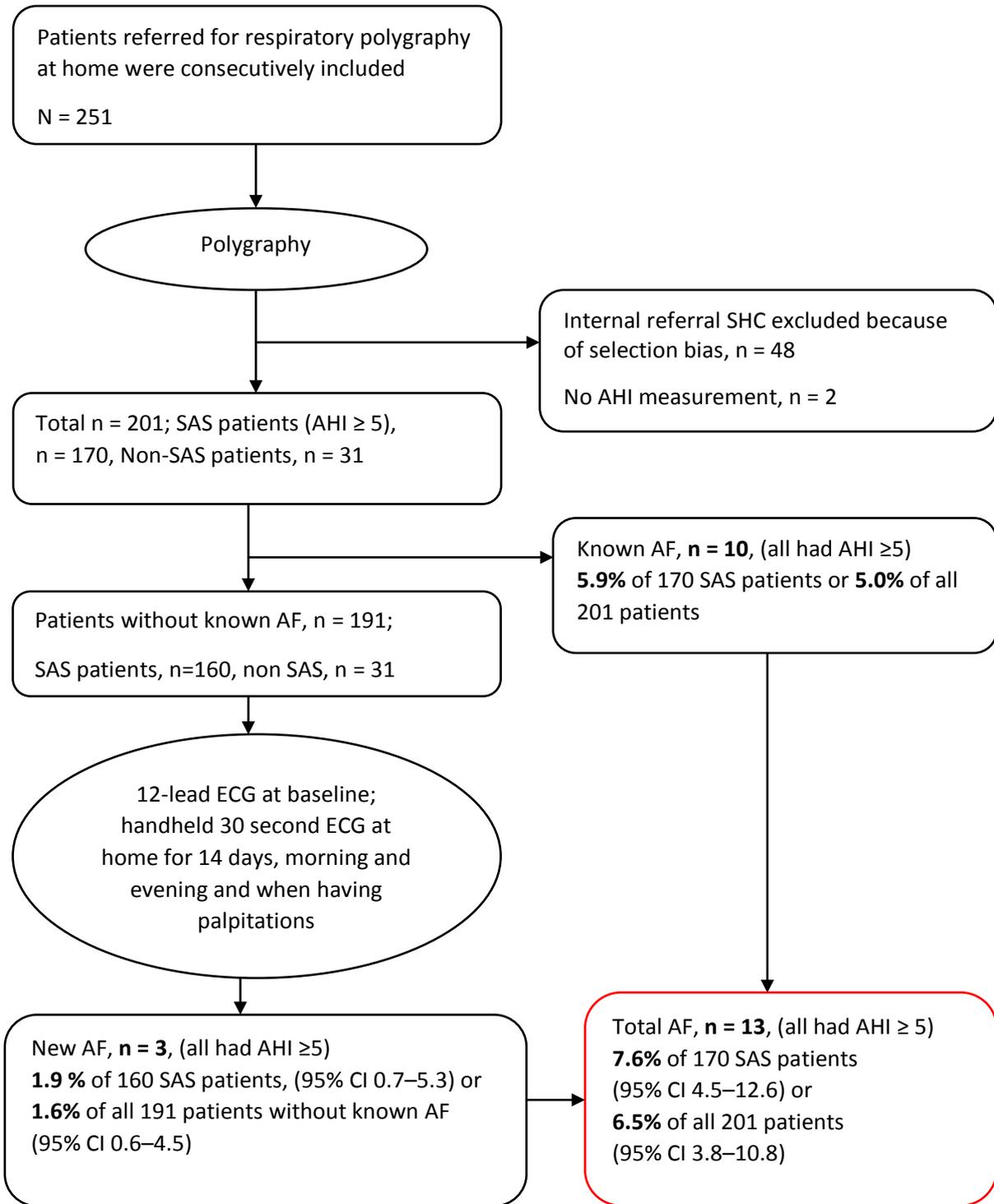


Figure 8. Flowchart paper IV.

Statistical analysis

SPSS Statistics 19/22 (IBM Corporation, Route 100 Somer, NY 10589) was used for all calculations. The level of significance was set at 0.05, two-sided.

In **all four papers**, continuous variables were presented with mean, standard deviation (SD), and range (minimum and maximum) whereas categorical variables were presented with count and percentage and, where appropriate, a 95% confidence interval.

Pearson Chi Square test was used to test for differences in AF detection rate for categorical variables. To evaluate possible differences in continuous and ordinal variables between individuals with and without detected AF, the Mann-Whitney U test was used. A statistician was consulted in all papers.

In **paper II** we used McNemar's test for paired proportions to test the hypothesis that there is a difference in the efficacy of intermittent ECG recordings compared to 24-hour Holter monitoring in detecting relevant arrhythmias.

In **paper III** binary logistic regression was used for multivariate analysis, comparing patients with enlarged and normal LA and patients with and without new paroxysmal AF. Ordinary one-way ANOVA and Kruskal-Wallis test for one-way ANOVA were used to compare LA volumes of patients without AF, with paroxysmal and with persistent AF.

In **paper IV** binary logistic regression was used for both univariate and multivariate analysis comparing patients with and without AF, and variables were presented as Odds Ratio (OR) and 95% confidence interval (CI).

Sample size

In **paper I** the sample size was based on the hypothesis of finding 4% AF. Given 1000 patients, this would yield a 95% confidence interval of $\pm 1\%$, which was deemed narrow enough to answer the objective.

In **paper II** the study was dimensioned to detect clinically relevant discrepancies between the two methods based on the following population effect size: in 80% of the patients, both methods will classify a patient as negative for a relevant arrhythmia and in another 3% both methods will classify a patient as positive. A discrepancy between the methods was assumed in the population as follows: in 14% of all patients only one test will show an outcome of positive relevant arrhythmia, while 3% of all patients will show an outcome of positive relevant arrhythmia for the other method. We needed 90 patients to yield a power of 80% with a statistically significant result with alpha of 0.05 (two-tailed). Calculating with a dropout rate of 15%, 106 patients needed to be included.

In **paper III** we assumed that we would find 8% AF in the group with enlarged LA and 4% in the control group. Power analysis (power of 80% and significance level of 0.05 (two-sided)) asked for 500 patients in both groups. As no differences in AF detection were seen after 300 patients, the study was discontinued. An additional comparison group of 29 patients with persistent AF (duration >10 months), matched for age with the original study population and matched for sex ratio with the Swedish AF population at age 71, was included in the study.

Group size was estimated given the assumption that these patients would have a mean LA index volume (ml/m²) of at least 40 with a power of 0.8 and significance level of 0.05 (two sided).

In **paper IV** the sample size was estimated at 146 patients plus 22 for potential loss, thus 168 patients to detect a significant difference of $p < 0.05$ with a power of 80% if the frequency of atrial fibrillation was 5% among patients with sleep apnea and 1.5% in patients without sleep apnea.

Ethical considerations

All studies comply with the Declaration of Helsinki. All actively participating patients gave written consent. We considered that there is no relevant risk with the actual investigation for the research subjects. In case of oral anticoagulation treatment as a result of the study the benefits for patients in general are greater than any possible risk. This is well established in previous studies and is in line with national guidelines from 2013 (Socialstyrelsen) and international guidelines from 2010 and 2012 (ESC). **Studies I, II, and III** were approved by the Regional Ethical Review Board in Umeå (Dnr 07-051M with an adaptation for **study III** (Dnr 2011-85-32M). **Study IV** was approved by the Regional Ethical Review Board in Stockholm (Dnr 2012/932-31/4 with adaptation Dnr 2012/1763-32).

RESULTS

An overview of the main results of all four papers is presented in Table 7.

Table 7. Main results in the four studies of this thesis

Paper	I	II	III	IV		
Included patients [n]	928	95	299	201		
Mean age [years]	69.8	54.1	73.1	56.3		
CHADS ₂ [median (range)]	2 (1–5)	0 (0–4)	2 (1–6)	1 (0–5)		
CHA ₂ DS ₂ -VASc [median (range)]	-	1 (0–6)	4 (1–8)	1 (0–6)		
Symptomatic patients	No	Yes	No	No		
		24h Holter ECG	Handheld ECG	Enlarged left atrium	Normal left atrium	
Known AF	Excluded	Excluded	Excluded	10 of 201 = 5.0%		
Detection of previously unknown AF	35 of 928 = 3.8% (95% CI 2.7–5.2)	2 of 95 = 2.1%	9 of 95 = 9.5%	Index diameter (mm/m ²)		3 of 191 = 1.6% (95% CI 0.6–4.5) 3 of 160 SA patients = 1.9% (95% CI 0.7–5.3)
				2 of 86 = 2.3% (95% CI 0.7–8.1)	9 of 213 = 4.2% (95% CI 2.3–7.8)	
				Index volume (ml/m ²)		
				5 of 153 = 3.3% (95% CI 1.4–7.4)	3 of 94 = 3.2% (95% CI 1.2–9.0)	
Total AF (known and previously unknown)						13 of 201 = 6.5% (95% CI 3.8–10.8) 13 of 170 SA patients = 7.6% (95% CI 4.5–12.6)
						6 of 17 SA patients with CAHI ≥5 = 35.3% (95% CI 17.3–59) 7 of 153 SA patients with CAHI <5 = 4.6% (95% CI 2.3–9.1)
PSVT		0	3 of 95 = 3.2%			
AV-block II		1 of 95 = 1.1%	1 of 95 = 1.1%			
Total relevant arrhythmias		3 of 95 = 3.2% (95% CI 1.1–8.9)	13 of 95 = 13.7% (95% CI 8.2–22.0)			
Mean atrial index volumes				Non-AF	Paroxysmal AF	Persistent AF
				32.1 ml/m²	31.6 ml/m²	48.4 ml/m²

Paper I

Demographics

A total of 989 patients, 491 men and 498 women, entered the study. Forty-nine patients with fewer than 20 recordings did not complete registration because of technical or medical problems. Twelve patients were excluded due to initial inappropriate inclusion (Figure 5. Study flowchart). Patients had a mean age of 69.8 and median CHADS₂ of 2 (range 1–5).

Detection of AF and AF characteristics

Analysis of our data showed newly diagnosed AF in 35 of these 928 patients (3.8% (95% confidence interval [CI] 2.7–5.2)). Twenty-eight (3.0%) of these AF patients were detected with handheld ECG alone. (Example of handheld ECG registration of AF, figure 4.)

Nine patients (1.0%) at the time of their first handheld ECG recording, nineteen patients (2.0%) during their 28 days of intermittent handheld ECG recording. Follow-up showed that of nine patients discovered at day one, six had persistent AF and three paroxysmal AF. On average AF was diagnosed after 7.3 days (SD \pm 7.6; range 1–28). One additional patient who continued with registrations after day 28 had one AF episode at day 38. As this was not detected within 28 days he was not counted as newly diagnosed AF within the study framework (Figure 9. Time to detection).

Seven patients (0.8%) showing episodes of repetitive irregular supraventricular extrasystoles (SVES) less than 10 seconds on handheld registrations were diagnosed with AF after an additional 24-hour Holter ECG. More than 80 percent of AF patients discovered with handheld ECG were found within 14 days. Four patients had atrial flutter. In case of typical p-wave morphology, as in atrial flutter, diagnosis was confirmed with 12-lead ECG or Holter ECG.

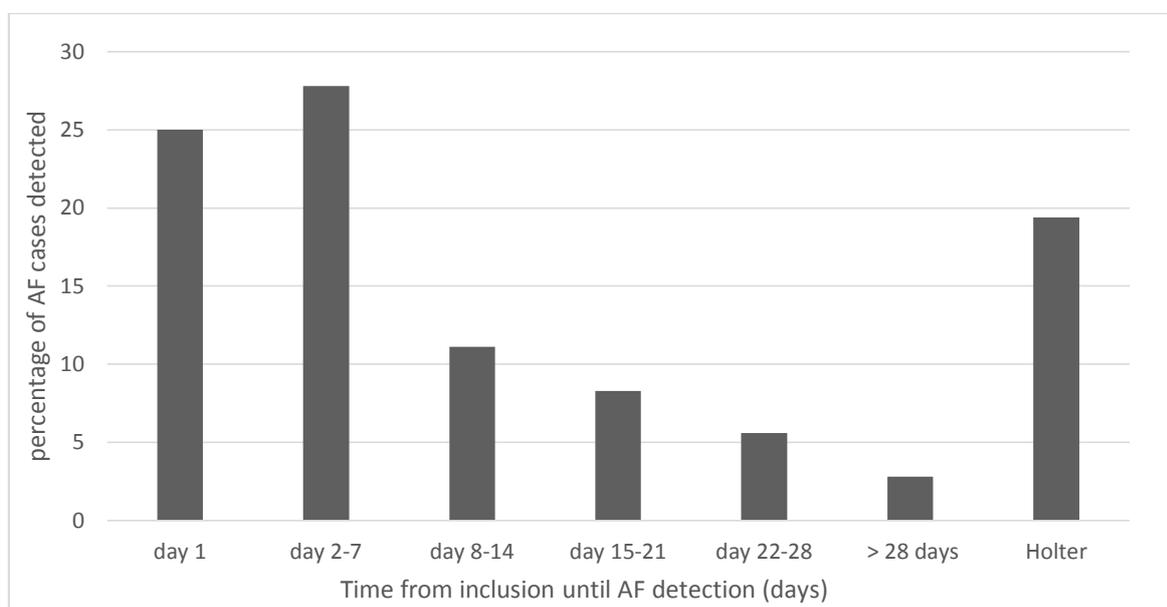


Figure 9. Time to detection of AF.

Eighty percent of patients with detected AF were aged ≥ 65 years. The AF detection rate for patients < 65 years was 2.9% and for patients ≥ 65 years 4.1% (Pearson Chi Square test, $p = 0.404$). For men prevalences in both age categories were 4.0% and 4.8% respectively ($p = 0.723$) and for women 1.1% and 3.5% ($p = 0.223$) (Figure 10). The patients in this study had low CHADS₂ scores in general with a median of 2 (range 1–5). Slightly higher detection rates for AF could be seen among those with CHADS₂ ≥ 2 compared to those with a score of 1, but no significant differences were seen ($p = 0.351$). More male than female patients were discovered (4.6% and 3.0% respectively), but this difference was not significant ($p = 0.218$).

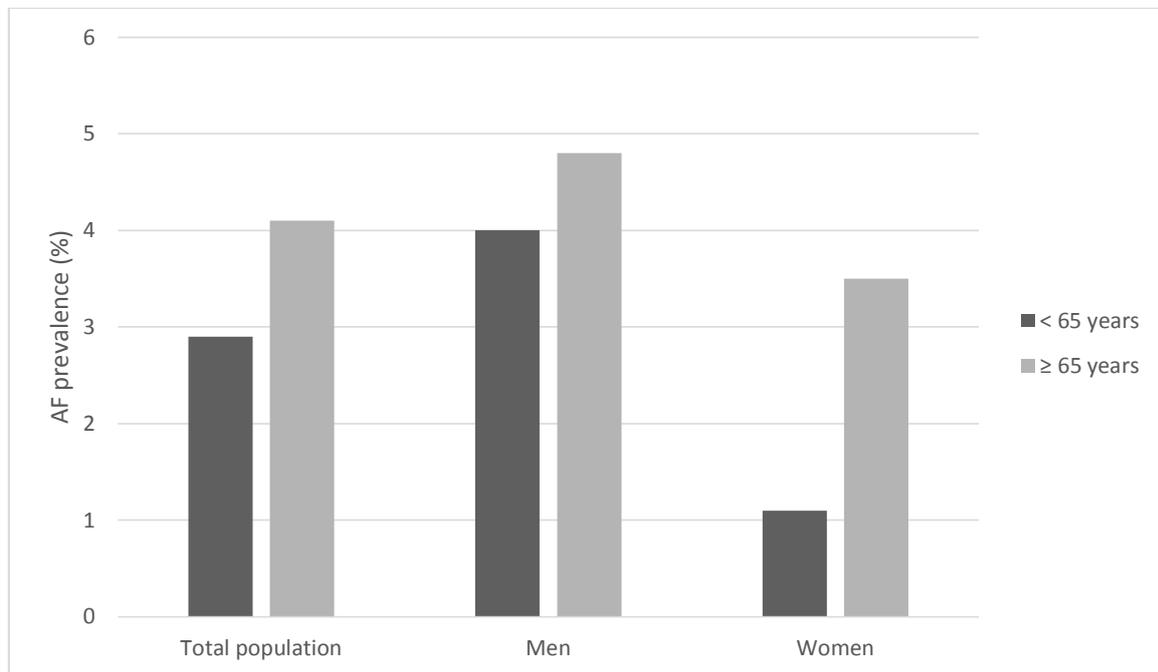


Figure 10. AF prevalence (%) per age category.

AF patients had AF in 33.7% of their registrations on average (SD ± 41.1 and range 1.3%–100%). AF paroxysms were equally distributed between morning and evening registrations. Only 12.4% of AF registrations were symptomatic.

Additional Holter ECG investigation

Thirty additional Holter investigations were done. Twenty-four Holter recordings were made, because of suspected AF on handheld ECG, and resulted in seven more AF diagnoses. Four of these patients had episodes of more than 30 seconds on Holter; three had episodes of more than 10 seconds but less than 30 seconds. Six Holter investigations were done because of suspected brady-arrhythmias. Five patients received a pacemaker because of diagnosis of AV block II–III or sinus arrest. These five patients had a CHADS₂ of 2, mainly as a result of hypertension and age ≥ 75 . Three of them had ischemic heart disease. Their mean age was 74.4 years with a range of 58–85.

Paper II

Demographics

Ninety-five patients, 42 men and 53 women with a mean age of 54.1 years, completed registrations. Thirteen of the originally included 108 patients were excluded after initial inappropriate inclusion; they either had a known tachyarrhythmia (n = 8) or suffered from syncope (n = 5) (Flowchart, figure 6). Of these 95 patients, 80 were referred for palpitations and 15 for dizziness/presyncope. Seventy-seven patients were referred by a primary health care center and 18 by a hospital clinic. Patients had a median CHA₂DS₂-VASc of 1 (range 0–6).

Both handheld and Holter registrations were of good quality. Only 1.6% of handheld registrations (84 of 5229 registrations) and 1.3% of Holter registrations (30 of 2280 hours) were of non-analyzable quality.

Detection of relevant arrhythmias

Analysis of the 24-hour Holter recordings showed AF in two patients and AV-block II in one patient, resulting in a total of 3.2% relevant arrhythmias (95% CI 1.1–8.9) detected. Nine patients with AF were detected with intermittent ECG. Two of these were the same as those discovered with Holter ECG; one of them had persistent AF. Two AF patients also had episodes with a fast regular rhythm, either atrial flutter or PSVT. Three patients were diagnosed with PSVT and one patient with AV-block II. One additional patient who continued with registrations on his own initiative after day 28 had an AF episode at day 50. As this was not detected within 28 days he was not counted as newly diagnosed AF within the study framework. In total 13.7% relevant arrhythmias (95% CI 8.2–22.0) were detected with intermittent handheld ECG. The statistical analysis showed a significant difference between the two methods in favor of intermittent handheld ECG recordings with regard to the ability to detect relevant arrhythmias (p = 0.0094) (Figure 11).

All arrhythmia episodes during Holter were asymptomatic. Forty-four percent of all arrhythmia episodes with intermittent recording were asymptomatic.

Results

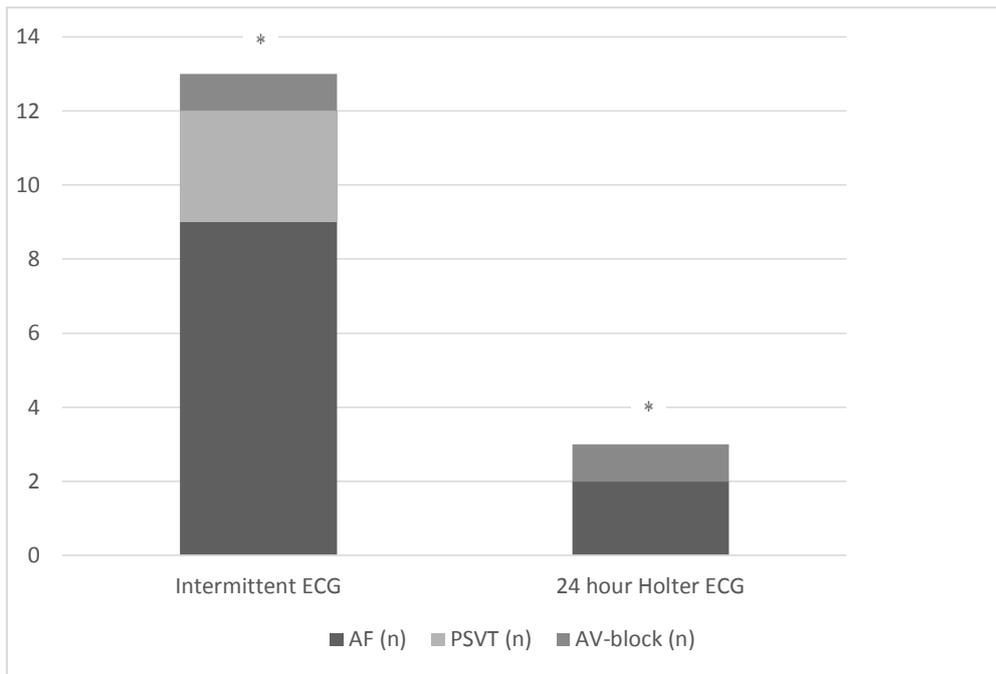


Figure 11. Comparison of intermittent and 24-hour Holter.

* Intermittent ECG significantly better at detecting relevant arrhythmias ($p = 0.0094$)

Atrial fibrillation

With nine AF patients detected with intermittent handheld ECG, AF was the main arrhythmia recorded. One AF patient was found on day one and the last AF patient was found on day 26. Two AF patients, one of them with persistent AF, were also discovered with Holter ECG. Patients with AF were slightly older and had slightly higher CHA₂DS₂-VASc scores compared to those without AF, but these differences were not statistically significant. Out of a median 61 intermittent registrations for AF patients (mean 62; SD ± 17.8 ; range 48-89), nine (median) were symptomatic ($9/61 = 14.8\%$) (mean 7.3; SD ± 5.2 ; range 0-16). These nine patients had four registrations (median) that showed AF ($4/61 = 6.6\%$) (mean 9.3; SD ± 18.3 ; range 1-61). All AF patients had a CHA₂DS₂-VASc ≥ 1 and were therefore potential candidates for oral anticoagulation treatment. All AF patients were referred for 24-hour Holter because of palpitations. No statistically significant differences were seen between the AF and non-AF groups for duration and number of palpitation episodes during the last 12 months before the study.

Paroxysmal supraventricular tachycardia

PSVT was detected in three patients with handheld ECG with a mean heart rate of 177 bpm (SD ± 18.8 , range 154-200). In two patients at least one episode was symptomatic (Example of handheld ECG registration of PSVT, figure 4). All PSVT patients were referred for 24-hour Holter because of palpitations.

Atrioventricular block II

One patient with AV-block II, discovered with Holter, was referred for Holter because of palpitations, the other, discovered with intermittent ECG, because of dizziness/presyncope. None of these patients had symptoms related to the recorded arrhythmia.

Paper III

Demographics

A total of 299 patients, 142 men and 157 women, with an average age of 73.1 years were included (Figure 7. Flowchart). Eighty-six (28.8%) patients had an enlarged and 213 (71.2%) a normal size LA according to index diameter (cm/m²). According to LA index volume (ml/m²) 153 (61.9%) had an enlarged and 94 (38.1%) a normal LA. On average patients had a normal LA diameter of 2.2 cm/m² and a slightly enlarged LA volume of 32.1 ml/m². In 52 patients (17.4%), LA volume could not be determined. Missing data analysis did not show any statistical differences for sex, age or LA diameter between these 52 patients and the remaining 247. Ejection fraction (EF), LA strain and BNP measurements showed normal values on average. Nearly a third (31.4%) of all patients were referred by primary care. More than 80% had hypertension and more than 20% an earlier stroke/TIA or other thromboembolic event. About half of the patients were taking beta-blockers, platelet inhibitors and/or ACE inhibitors/ARBs. Seventeen patients (5.7%) were on oral anticoagulation because of deep venous thrombosis or pulmonary emboli. Patients had a median CHA₂DS₂-VASc score of 4 (range 1–8).

Detection of AF, comparing large and normal size LA

Eleven new paroxysmal AF patients were found, five men and six women. Two of these had an enlarged LA according to index diameter and five according to index volume. No statistical difference in AF prevalence was seen between patients with enlarged and normal LA index diameter (2.3% (95% CI 0.7–8.1) versus 4.2% (95% CI 2.3–7.8), $p = 0.43$) and enlarged and normal index volume (3.3% (95% CI 1.4–7.4) versus 3.2% (95% CI 1.2–9.0), $p = 0.974$) respectively. Patients with enlarged LA had an average index volume of 37.5 ml/m² compared with 23.3 ml/m² for patients with a normal size LA. Patients with an enlarged LA index volume had statistically higher BNP levels ($p = 0.011$) and reduced LA strain ($p = 0.001$). At a multivariate level, no other statistical significances were seen. Although left ventricle (LV) EF did not differ between the groups, other measurements taking global LV dysfunction, reduced ejection fraction, movement disorder, increased filling pressure, and pulmonary hypertension into account showed significantly decreased left ventricle function in patients with enlarged LA (40.5% versus 26.6% in normal LA). Patients with enlarged LA also had more valvular disease (60.8 versus 43.6%), but the large majority of these only had minor valvular disease (grade I insufficiency or stenosis) in both groups.

Comparison of new, paroxysmal AF patients and non-AF patients

No significant differences were seen in patient groups with and without AF except that AF patients were to a higher extent (63.6% versus 30.2%, $p = 0.04$) referred from primary care. The detection rate of new AF in patients referred from primary care was 7.4%.

LA volumes and diameters in non-AF, paroxysmal AF and persistent AF

A comparison group of 29 patients with known persistent AF (duration >10 months) was additionally examined. Patients were matched for age with the original study population ($n = 299$) and matched for sex ratio with the Swedish AF population at age 71 (SBU report 2013, data from the Swedish National Patient Register). LA index volumes between the three groups with non-AF, new, paroxysmal AF and persistent AF were compared. Index volumes were significantly increased in persistent AF patients compared to both other groups. (Persistent versus paroxysmal AF $p = 0.0005$ and persistent versus non-AF $p < 0.0001$)

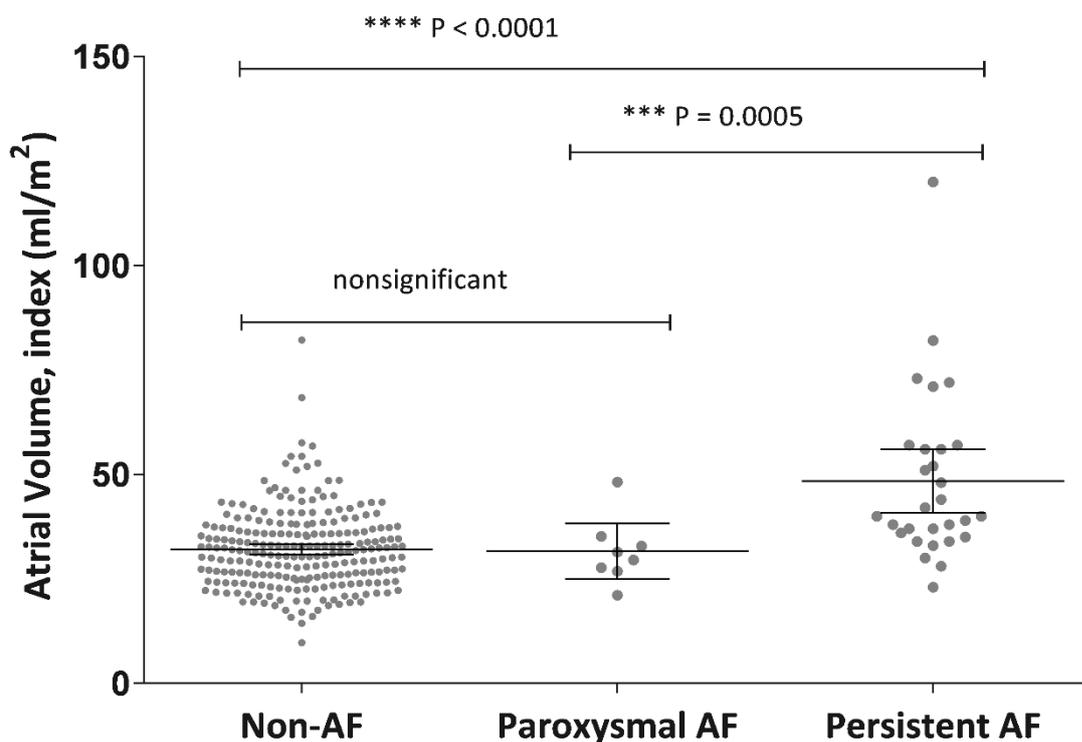


Figure 12. One-way Anova of atrial volume, index (ml/m^2), means and 95% CI, for non-AF, paroxysmal AF and persistent AF

BNP analysis

Mean BNP in the study population was 77.8 pg/ml. Sixty-one patients had an elevated BNP, ≥ 100 pg/ml. Only three patients had a BNP ≥ 500 pg/ml. Patients with an enlarged left atrium had significantly higher BNP values in comparison with patients with a normal size left atrium. Mean values were 99.8 versus 44.3 pg/ml ($p=0.000$). AF patients did not show a

tendency to have increased BNP values. When comparing patients with paroxysmal AF with patients without AF no significant difference was seen, ($p=0.859$).

PAPER IV

Demographics

Two patients failed to complete cardiorespiratory polygraphy and were excluded (Figure 8, Flowchart). 48 patients referred by Stockholm Heart Center for sleep apnea investigation were also excluded as there seemed to be a serious selection bias. Patients seemed to be included for sleep apnea investigation not because of symptoms of obstructive sleep apnea, but because of presence of heart disease. Half of these 48 patient had known AF. Included were 201 patients with an average age of 56.3 years. Almost 70% were men (Table 8). One hundred and seventy (85%) had sleep apnea with an apnea-hypopnea index ≥ 5 . All except one had obstructive sleep apnea. Seventeen patients had central sleep apnea and 16 of these also had obstructive sleep apnea. Thirty-one patients did not have sleep apnea. About 80% were referred for sleep apnea investigation by a primary care center, 20% by a hospital clinic. Patients had a median CHA₂DS₂-VASc of 1, ranging from 0–6 and more than 50% had a hypertension diagnosis. Blood pressure was on average well regulated (mean 133/82 mmHg). Patients were moderately obese with a mean BMI of 30.1 kg/m². Few patients were smokers (8.1%). Patients had an average amount of daytime sleepiness on the Epworth sleepiness scale (8.8), a high mean AHI (23.2 episodes/hr) and ODI (24.9 episodes/hr).

Table 8. Demographic characteristics of 201 studied patients.

Men [n, (%)]	138	(68.7)	
Age [years, mean, SD, (range)]	56.3	± 12.2	(21–86)
Referral primary care	162	(80.6)	
Hospital clinic referral	39	(19.4)	
Heart Failure [n, (%)]	9	(4.6)	
Hypertension [n, (%)]	101	(51.3)	
Diabetes mellitus [n, (%)]	20	(10.2)	
Stroke/TIA [n, (%)]	6	(3.1)	
Ischemic heart disease [n, (%)]	18	(9.2)	
CHA ₂ DS ₂ -VASc [median, (range)]	1	(0–6)	
Systolic blood pressure [mmHg, mean, SD, (range)]	132.6	± 14.6	(100–180)
Diastolic blood pressure [mmHg, mean, SD, (range)]	82.1	± 10.1	(50–120)
BMI [kg/m ² , mean, SD, (range)]	30.1	± 5.4	(19.8–49.2)
Smoking [n, (%)]	16	(8.1)	
Epworth sleepiness scale [mean, SD, (range)]	8.8	± 5	(0–21)
AHI [episodes/hr, mean, SD, (range)]	23.2	± 19.6	(0–92)
AHI ≥ 5	170	(84.6)	
CAHI ≥ 5 [n, (%)]	17	(8.6)	
ODI [episodes/hr, mean, SD, (range)]	24.9	± 19.7	(0–95.4)

Comparison of patients with and without AF

Ten (5.9%, 95% confidence interval [CI] 3.3–10.5) of the sleep apnea patients had a previous diagnosis of AF. Of the 160 sleep apnea patients without known AF, one patient had AF on 12-lead resting ECG. Two more had AF during hand-held ECG screening, resulting in three new AF cases, 1.9% (95% confidence interval [CI] 0.7–5.3). In total, thirteen of 170 subjects (7.6%) with sleep apnea had AF (95% confidence interval [CI] 4.5–12.6). There were no AF cases in the non-sleep apnea group. Characteristics of AF and non-AF patients are shown in Table 9.

Table 9. Predictors of atrial fibrillation (n=201 patients).

	AF, n = 13	Non-AF, n = 188	p-value*
Men, [n, (%)]	13, (100)	125, (66.5)	0.012
Age [years, mean, SD, (range)]	69.5, ±9.6, (58–86)	55.3, ±12, (21–80)	0.000
Age ≥60 [n, (%)]	13, (100)	106, (56.4)	0.002
Age ≥65 [n, (%)]	10, (76.9)	40, (21.3)	0.000
Age ≥75 [n, (%)]	2, (15.4)	12, (6.4)	0.218
Referral primary care	9 (69.2)	153 (81.4)	0.284
Heart Failure, [n, (%)]	1, (7.7)	8, (4.4)	0.580
Hypertension, [n, (%)]	8, (61.5)	93, (50.5)	0.443
Diabetes mellitus, [n, (%)]	4, (30.8)	16, (8.7)	0.011
Stroke/TIA, [n, (%)]	2, (15.4)	4, (2.2)	0.008
Ischemic heart disease [n, (%)]	5, (38.5)	13, (7.1)	0.000
CHA ₂ DS ₂ VASc [median,(range)]	3, (0–6)	1, (0–6)	0.000
Systolic blood pressure [mmHg, mean, SD, (range)]	124.1, ±14.7, (105–160)	133.2, ±14.4, (100–180)	0.011
Diastolic blood pressure [mmHg, mean, SD, (range)]	75.5, ±18.9, (50–120)	82.5, ±9.1, (60–120)	0.036
BMI [kg/m ² , mean, SD, (range)]	27.5, ±1.9, (25.3–31.4)	30.3, ±5.5, (19.8–49.2)	0.068
Smoking, [n, (%)]	2, (15.4)	14, (7.6)	0.321
Epworth [mean, SD, (range)]	9.6, ± 5.3, (3–19)	8.8, ± 5.0, (0–21)	0.728
AHI [episodes/hr, mean, SD, (range)]	27.4, ± 12.2, (10–43.9)	22.9, ± 20.0, (0–92)	0.100
AHI ≥5	13 (100)	157 (83.5)	0.111
CAHI ≥5 [n, (%)]	6 (46.2)	11 (5.9)	0.000
ODI [episodes/hr, mean, SD, (range)]	26.9, ± 11.7, (10–46.3)	24.7, ± 20.1, (0–95.4)	0.185

*calculated with Pearson Chi Square test for categorical variables and Mann-Whitney for continuous and ordinal variables.

AF occurred in 6 of 17 patients (35.3%) with central sleep apnea and in 7 of 153 patients (4.6%) with “pure” obstructive sleep apnea. All patients with AF were men and all had sleep apnea. The prevalence of AF increased with the severity of sleep apnea, ($p = 0.038$).

Presence of central sleep apnea ($p = 0.001$), age ≥60 years ($p = 0.043$) and diabetes mellitus ($p = 0.007$) were independently related to AF with adjustments for BMI, sleep apnea and

Results

cardiovascular disease including congestive heart failure, hypertension, ischemic heart disease, earlier stroke and previous transient ischemic attacks.

The prevalence of AF in sleep apnea patients increased with increasing age and AF occurred in 12 of 81 patients (15%) with sleep apnea aged 60 years and older (Figure 13).

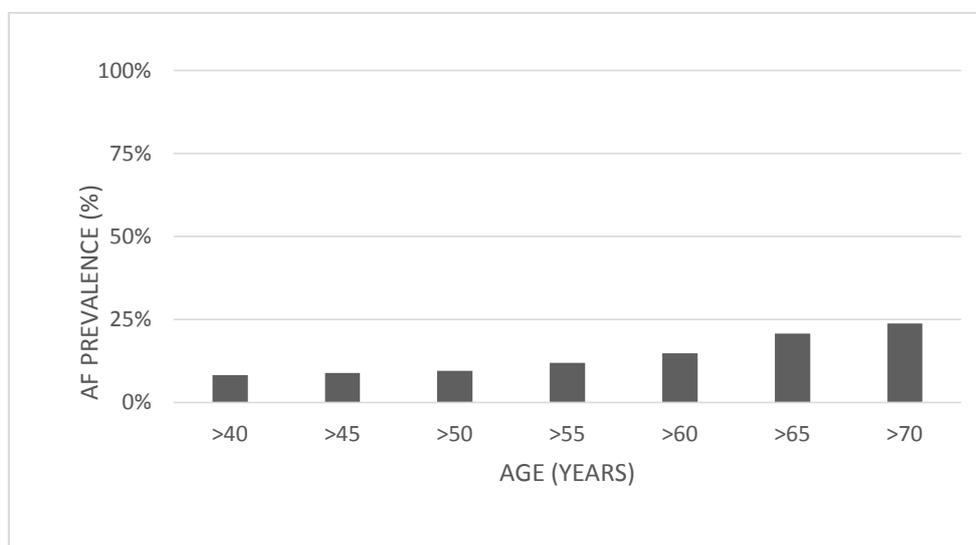


Figure 13. The prevalence of AF among 170 patients with sleep apnea in relation to age.

AF prevalence in the sleep apnea population in this study (n = 170) was elevated in comparison with AF prevalence in the general Swedish population (data from the National Patient Register, SBU report: Förmaksflimmer, förekomst och risk för stroke (AF, prevalence and risk for stroke), 2013), (Figure 14).

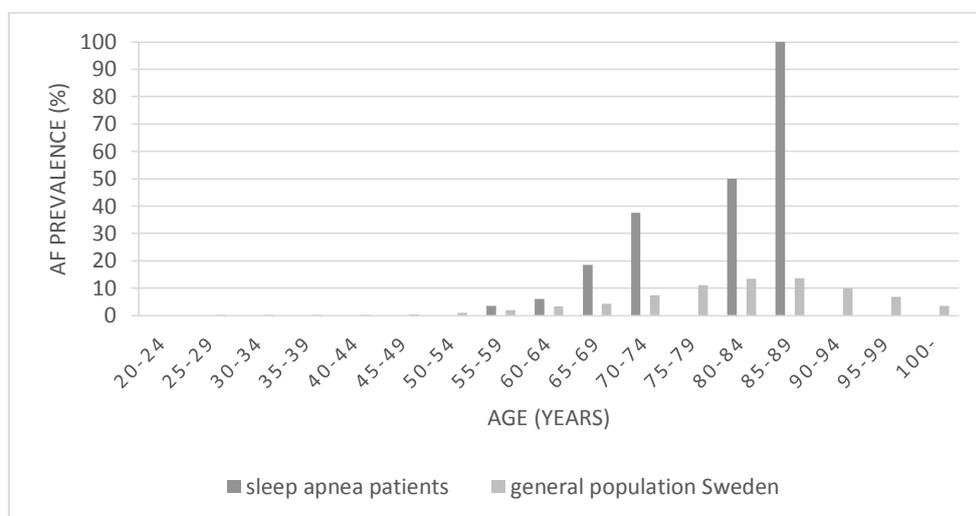


Figure 14. AF prevalence among 170 patients with sleep apnea for different age categories compared with the general population in Sweden. (Data from National Patient Register, SBU report: Förmaksflimmer, förekomst och risk för stroke (AF, prevalence and risk for stroke), 2013).

Results

The prevalence of AF among 17 patients with central sleep apnea (central apnea-hypopnea index ≥ 5) in relation to age is given in Figure 15. AF occurred in 6 of 11 patients (55%) with central sleep apnea aged 60 years and older

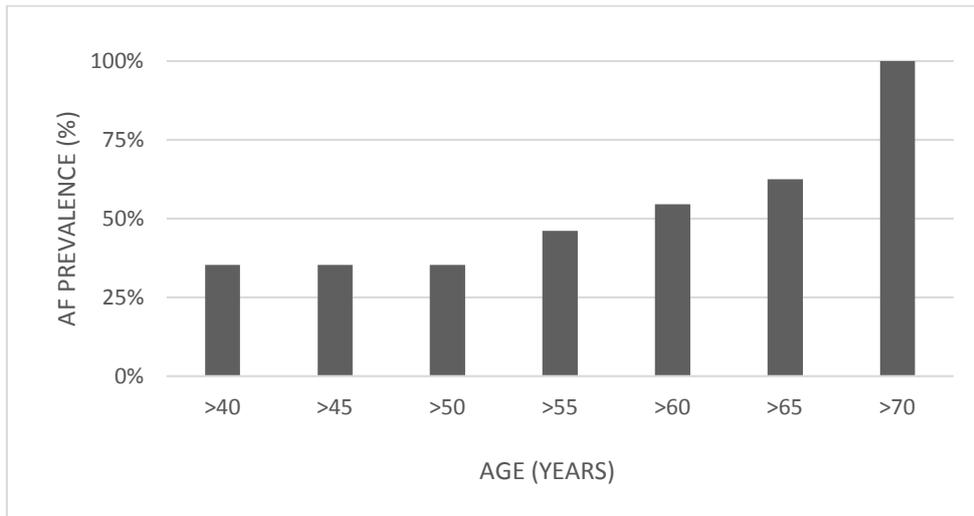


Figure 15. The prevalence of AF among 17 patients with central sleep apnea in relation to age.

DISCUSSION

This thesis contributes new knowledge about feasibility of AF screening with short, intermittent ECG recordings during several weeks, in different populations.

Main findings

This thesis shows that screening in a general out-of-hospital population with one or more risk factors associated with stroke ($\text{CHADS}_2 \geq 1$), using short, intermittent ECG recordings, both regular asymptomatic and symptomatic, detects almost 4% new AF cases, which is significantly more than the 1% found by earlier AF screening studies using pulse palpation and 12-lead ECG. It also demonstrates clearly that routine investigation with 24-hour Holter ECG of patients contacting health care with complaints of paroxysmal palpitations or dizziness/near-syncope should be phased out and that short, intermittent, ECG recordings during several weeks are an alternative that should be used more often. Furthermore, it suggests, that there is no use in specifically screening patients with an enlarged left atrium for AF, as detection rates are the same as in patients with a normal size left atrium. Finally, AF occurred in 7.6% of patients with sleep apnea among subjects investigated for suspected obstructive sleep apnea. All patients with AF were men and all had sleep apnea. Age ≥ 60 years, the occurrence of central sleep apnea and diabetes mellitus were risk factors for AF independent of body mass index, gender, sleep apnea and cardiovascular disease.

Methods and Results

Paper I

Opportunistic screening in an out-of-hospital population with at least one risk factor for stroke ($\text{CHADS}_2 \geq 1$) resulted in detection of 3.8% previously unknown AF, higher than in previous studies of out-of-hospital populations.¹⁰⁹⁻¹¹¹ These results, together with the results of a 2013 study from Halmstad screening 75-year-old patients, detecting 5.2% new AF and even 7.4% among those with $\text{CHADS}_2 \geq 2$ ²⁴, show the possibilities for the use of intermittent ECG registration as a screening instrument for detection of AF. A detection rate of 3.8% newly diagnosed AF is high, especially when considering that the study population was relatively young and healthy with few CHADS_2 risk factors. A survey of previously published studies did not reveal data comparing the efficiency of intermittent ECG recording with other screening methods for the detection of AF in an out-of-hospital population. A British multi-center randomized controlled trial using systematic and/or opportunistic screening with pulse control and 12-lead ECG to detect AF among people over 65 years found incidences of less than 2% newly diagnosed AF for all methods (even when including patients detected outside the screening program), within a year of screening.^{109, 110} Another

study screening a general practice population using pulse assessment found about 1% previously unknown AF¹¹¹, which is the same as the 1% new AF detection on the first day of recording in this study. Seven out of 35 new AF patients had to be confirmed with an additional 24-hour Holter ECG. Nevertheless, only 24 Holter recordings were done to find seven more AF cases, which makes this kind of intermittent screening still very efficient.

The usefulness of short intermittent ECG recordings has also been shown in screening post-stroke patients for AF. Earlier studies of post-stroke patients have estimated a prevalence of 3.8–8.4% previously undiagnosed AF using 24-hour Holter and Event loop recorder ECG⁷⁸⁻⁸⁰. A 2012 Swedish study showed that intermittent handheld ECG recording compared with 24-hour Holter ECG substantially improves the detection of silent paroxysmal atrial fibrillation (AF) in post-stroke patients.¹²¹

Continuous ECG recording during a long time period would most likely result in even more AF detection. In a 2012 study, continuous monitoring during a follow-up of 1.1 ± 0.7 years with an implanted device resulted in detection of 30% previously unknown AF, in a population of patients with risk factors for stroke, who had recently received a pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy device.¹³³ Of all 2580 pacemaker and defibrillator patients in the ASSERT study who experienced stroke or systemic embolism during follow-up, 26 (51%) had subclinical AF (SCAF). In 18 patients (35%), SCAF was detected before stroke or systemic embolism. The median duration of continuous device monitoring before embolic events was >1.7 years.²⁶ In the Crystal-AF study including 441 patients with a cryptogenic stroke. Patients were randomized either to an insertable cardiac monitor (ICM) or to conventional follow-up. By 6 months, AF had been detected in 8.9% of patients in the ICM group (19 patients) versus 1.4% of patients in the control group (3 patients). By 12 months, AF had been detected in 12.4% of patients in the ICM group (29 patients) versus 2.0% of patients in the control group (4 patients).¹³⁴ Using such implantable devices for screening in large out-of-hospital populations solely for the purpose of AF detection is at present not suitable for economic reasons. Other devices, e.g. patch-based appliances with the possibility of long-term continuous recording, could however become an alternative for screening in large out-of-hospital populations.¹³⁵

Study population, Representativeness, Compliance

A total of 1003 patients were asked to take part in the study (Flowchart, figure 5). Only 14 were not interested (1.4%). Of the remaining 989 patients, 49 patients (5%) made less than 20 recordings because of cognitive/other functional impairments or lack of motivation and 12 patients (1.2%) were excluded for not fulfilling inclusion criteria. Dropout was low, if we do not take patients that should not have been included into account, only 6.4%. The high response rate shows that the method used is acceptable to the population. People were actually very willing to participate and some even got annoyed when they were told that they could not participate as they had no CHADS₂ risk factors for stroke.

The study design does not allow for any assessment of representativeness. The detection rates of AF, mean age, and mean CHADS₂ were comparable at all ten centers. This together with the size of the study population, consecutive inclusion, a very high participation rate and low dropout, increases the likeliness of representativeness.

Compliance was high. The mean number of registrations per patients, with respect to a recommended number of 56 registrations, was 55 registrations (median 56, IQR 52–60). More than 95% of all included patients had a sufficient number of registrations.

Paper II

This study showed that intermittent ECG recording, during several weeks, is superior to routine 24-hour Holter ECG in detecting relevant paroxysmal arrhythmias in a patient population reporting symptoms of palpitations, dizziness/presyncope. The novelty in this study compared to other studies searching for paroxysmal arrhythmias is the use of prolonged intermittent recording for four weeks, both regularly twice daily and when having symptoms. To our knowledge, there are no earlier reports comparing brief intermittent long-term ECG with 24-hour Holter ECG directly in detecting paroxysmal arrhythmias in patients referred for ambiguous cardiac symptoms.

It was already known that the sensitivity of 24-hour Holter recordings for detecting relevant arrhythmias is low but it is still widely used as a routine in primary care and hospital settings. The fact that almost half of the intermittent recordings showing significant arrhythmias were recorded without associated symptoms emphasizes that this method even has advantages compared to standard event recording. At the same time it should be mentioned that it has been previously estimated that only one in ten paroxysms of AF is symptomatic.^{22, 25} The much higher rate, about fifty percent, of symptomatic episodes in this study may be explained by the fact that included patients are selected for having ambiguous cardiac symptoms.

Study population, Representativeness, Compliance

Out of the 95 patients included in the study, only two had fewer than 20 recordings. Thirteen of the original 108 patients (12%) were excluded, as they did not fulfill inclusion criteria. (See flowchart, figure 6).

Consecutive inclusion and the fact that the Department of Clinical Physiology is the only center in Västerbotten County for this type of service increases the likeliness of representativeness of the study population in comparison with patients contacting health care with complaints that might be caused by an arrhythmia (palpitations or dizziness/near-syncope) in general. Other studies investigating palpitations looking at a general population show quite similar characteristics for age, sex and comorbidity.^{115, 116, 136}

Compliance with the intermittent handheld ECG method was high. The 95 included patients had on average 55 registrations (median 59, IQR 49–65), which is about two registrations a day for 28 days. The high compliance rate using this method indicates that it is a feasible method for screening in larger patient populations.

Paper III

Less AF than expected was detected in the group with large index LA volume. Detection levels were the same as in the normal LA control group and comparable to other studies screening different selections from the general population for AF using the same method.^{24, 129, 137} These results suggest that it is not worthwhile to screen patients with a large LA for new AF, at least not in the volume range being studied here.

Study population, Representativeness, Compliance

Of the 299 patients included in the study, none had fewer than 20 recordings. Only one of the original 300 patients (0.3%) was excluded, as he did not fulfill inclusion criteria (Flowchart, figure 7).

Consecutive inclusion and the fact that the Department of Clinical Physiology, as in paper II, is the only center in Västerbotten County for this type of service increases the likeliness of representativeness of the study population in comparison with patients with an enlarged left atrium in general.

Compliance with the handheld device was high, and patients made on average 62 recordings (median 62, IQR 58–65) which is slightly more than two a day during four weeks.

Interestingly, those patients where we detected new AF came largely from primary care. One possible reason for a higher detection rate of AF in this subgroup (7 out of 94 patients; 7.4% compared to only 2% in the patients referred by hospital clinic; $p = 0.019$) could be that the patients referred from primary care had been less extensively investigated. Patients coming from hospital clinics are in general less healthy and more thoroughly examined, having already done more ECG investigations, which makes the chances of finding new AF less likely.

Cardiac ultrasound measurements in study III

With cardiac ultrasound both atrial volume and diameter were measured. Detection rates and ratios for AF between large and normal LA were comparable for both diameter and volume. Diameter and volume were converted to index diameter and volume by taking body surface area (BSA) into account. Unindexed diameter measurements showed a clear overrepresentation of tall men in the large LA group. Indexed diameter measurements, on the other hand, seemed to overrepresent small women. As a result, we decided to focus on indexed volume, giving the most reliable view of atrial enlargement. Indexed volume (ml/m^2) has also been recommended as the measurement of choice and is well validated.¹³⁸

Results were not as expected, and because of this, the study was discontinued after an interim analysis of 300 patients. As a result, numbers are smaller than planned, which makes the analysis of subgroups statistically less robust.

We collected data on both diameter and volume. Diameter measurements are complete without any missing values, but seem to underestimate actual LA enlargement. Volume data are not complete because image quality hindered biplane measurements. Patients without

volume measurements, however, did not show any statistical differences for sex, age, AF detection and diameter compared with the remaining patients.

As patients in the comparison group with persistent AF (>10 months) had significantly greater LA volumes compared with both non-AF patients and patients with paroxysmal AF, data seem to suggest that early paroxysmal AF precedes LA enlargement. Firm conclusions cannot be drawn, as numbers are too small to compare AF burden and the development of LA enlargement over time.

In this study, BNP was, as expected, elevated in patients with an enlarged left atrium compared to patients with a normal size left atrium. BNP was not elevated in patients with paroxysmal AF compared to patients without AF and can therefore not be considered as a predictor of paroxysmal AF. As numbers of AF patients in this study were small (n = 11) some caution should be used when drawing conclusions.

Paper IV

The frequency of sleep apnea among patients with AF has been comprehensively studied; however, the frequency of AF in sleep apnea has only been investigated in two previous studies. Chanda et al. investigated 20 patients with severe sleep apnea during 7 days with ambulatory ECG event recordings and observed one patient with paroxysmal AF.¹³⁹ Leung et al. investigated a subsample of 60 patients with idiopathic central sleep apnea without congestive heart failure, coronary artery disease or a previous stroke and 60 patients with obstructive sleep apnea.¹⁴⁰ They recorded AF during the whole night in 27% of patients with central sleep apnea and in 1.7% of patients with obstructive sleep apnea from a single ECG lead attached to the sleep apnea recordings.

In this study we investigated a sample of non-selected patients being referred for suspected sleep apnea and observed a higher prevalence of AF; 35.3% in patients with central sleep apnea and 4.6% in patients with obstructive sleep apnea. A reason for the higher prevalence of AF in the present study compared with the above-cited study by Leung et al. could be that we did not exclude patients with cardiovascular disease and that we searched for undiagnosed AF using handheld ECG at home, during 14 days.

Obstructive sleep apneas are followed by surges of sympathetic activity, an increase in blood pressure during apnea and a decrease in blood pressure and hypoxemia after apnea⁶⁰⁻⁶² A number of studies have suggested that obstructive sleep apnea is a risk factor not only for cardiovascular disease^{63, 64, 141-144}, but also for AF^{66, 67, 145}, and observed sleep apnea in 80% of patients with AF.^{66, 67} Central sleep apnea, on the other hand, is generally considered the result of congestive heart failure or stroke^{65, 69, 70}, because of hypocapnia, reduced cardiac output and enhanced sensitivity to carbon dioxide.^{69, 71} AF is related to central sleep apnea

in heart failure patients⁷¹, and it is suggested that AF is a risk factor for central sleep apnea because it further deteriorates cardiac output.

Both AF and obstructive sleep apnea are risk factors for stroke. AF was common among patients with sleep apnea in the present study especially among men older than 60 years and among men with central sleep apnea. The evidence of treatment with oral anticoagulation to prevent stroke is strong among patients with AF^{16, 17} and it is therefore important to search for AF among patients at risk who are investigated for suspected sleep apnea.⁷²

Study population, Representativeness, Compliance

Patients, referred for cardiorespiratory polygraphy, were randomly assigned for inclusion at days when a study nurse and equipment for atrial fibrillation detection was present. Random assignment increases the likeliness of representativeness of the study population in comparison with sleep apnea patients in general. A selection bias was noticed in the material from Stockholm Heart Center (SHC), where patients seemed to be referred (internal referral SHC) not because of complaints related to obstructive sleep apnea, such as snoring and apnea but because of presence of heart disease. Therefore these 48 patients, (24 with known AF), were excluded.

Compliance with the handheld device was high, and patients made on average 29 recordings (median 30, IQR 28–32) which is slightly more than two a day during two weeks.

Cardiorespiratory polygraphy in study IV

Cardiorespiratory polygraphy at home as used in our study is a simplified sleep apnea recording without EEG recordings of sleep time. Sleep time is approximated as recording time or time-in-bed. Because time-in-bed is usually longer than sleep time, this approach introduces a risk of underestimating the average number of obstructive events per hour of sleep and thus underestimating the number of sleep apnea patients. It is therefore of importance to have specially trained personnel, as in this study, to score registrations manually.

General discussion

One strength of the method used in these studies with short (10–30 seconds) recordings during several (2–4) weeks with both regular asymptomatic and symptomatic recordings is that we were able to detect both symptomatic and asymptomatic arrhythmia episodes. Detection of asymptomatic episodes is relevant considering that previous studies have estimated that only one in ten paroxysms of AF is symptomatic.^{22, 25}

The length of the recording period of several weeks is another strength, because the longer you search for an arrhythmia the more you will find. For practical reasons, however, a limit

of two to four weeks seems reasonable when studying large groups of patients. In paper I, more than 80% of AF patients were also detected within 14 days.

Handheld ECG in combination with the chosen screening method has advantages compared to other traditional screening instruments. The device is small and involves almost no limitation to the mobility of the patients as no external electrodes are used. Registrations are easy to perform, which is also reflected in a high compliance rate. The ECG recording can immediately be transmitted to a website and assessed directly. The costs per screened patient are relatively low. The Dental and Pharmaceutical Benefits Agency (TLV) has estimated costs at SEK 954 SEK (€100) per patient. (Kunskapsunderlag: Hälsoekonomisk utvärdering gällande primärpreventiv screening av förmaksflimmer med tum-EKG, 2014, TLV).

A maximum recording time of 30 seconds, in study I only 10 seconds, is the main limitation of our method. As a result, we often did not know the duration of an arrhythmia episode. Continuous recording would most likely have resulted in more arrhythmia episodes being detected and probably even more new AF cases, but that would require another kind of device and would generate a lot more data to analyze. We do not know at present how relevant 10-second or 30-second registrations of AF, as used in guidelines, are. The AF definition used by the European Society of Cardiology in its Guidelines from 2010 “Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 s on a rhythm strip, should be considered as AF” is not empirical, but based on consensus.¹⁶ Standard 12-lead ECG is a 10-second strip and diagnosis of AF based on a 10-second 12-lead resting ECG is used in other recent studies.¹⁴⁶ A 2012 study enrolled 2580 patients, 65 years of age or older, with hypertension and no history of atrial fibrillation, in whom a pacemaker or defibrillator had recently been implanted. It monitored the patients for 3 months to detect subclinical atrial tachyarrhythmias (episodes of atrial rate >190 beats per minute for more than 6 minutes) and found that these short subclinical atrial tachyarrhythmias, without clinical atrial fibrillation, occurred frequently in patients with pacemakers and were associated with a significantly increased risk of ischemic stroke or systemic embolism.²⁵ Further analysis of the same ASSERT material, published in 2014, showed that although subclinical atrial fibrillation (SCAF) is associated with an increased risk of stroke and embolism, very few patients had SCAF in the month before their event.²⁶ So the relation between subclinical AF, AF burden in general, and risk of stroke and embolism is still not clear.

Providing lifelong anticoagulation to someone with a single 10- or 30-second episode of AF is definitely a leap too far at present. It is therefore important in future screening projects that patients complete the screening period even if AF is diagnosed and further confirmatory testing may be required in some patients.

The device does not allow for recording when sleeping, exercising, and during syncope. Other devices, e.g. patch-based appliances with the possibility of long-term continuous

recording, are most likely an even better alternative than devices for short intermittent recording, as these would not miss episodes during physical exertion, sleep, or syncope.¹³⁵ Smartphone-based applications, in view of their high accessibility, can also be expected to become useful tools for screening and monitoring of AF and other paroxysmal arrhythmias.^{126, 147, 148}

The handheld ECG device records only lead I, which sometimes makes it difficult to distinguish (1:1 and 2:1 blocked) atrial flutter from a regular supraventricular re-entry tachycardia such as AV-nodal re-entry tachycardia, which might have resulted in underdetection of atrial flutter.¹²² At the same time, we cannot exclude the possibility of some cases with short runs of atrial tachycardia being mislabeled as AF because of the short 10-second recording time.¹²²

Expected importance and future perspectives

General population screening

The high compliance rate using this method indicates that it is acceptable to the population as a screening instrument for AF. More than 80% of AF diagnoses with handheld ECG were found within 14 days in study I, suggesting that the registration period can be shortened without losing too much information. In a study from the same research group on a 75-year-old population from Halmstad, more than 7% new AF patients were discovered in the subgroup with CHADS₂ ≥ 2 within 14 days.²⁴ On the other hand, in paper II only 70% of arrhythmia cases and in paper III only 55% of AF cases were detected within 14 days. In paper IV patients were only screened 14 days.

An ideal future screening population would be a group with high prevalence of AF, a sufficiently high remaining life-expectancy and at high risk of stroke unless given protective treatment. Looking at the general population, we see that screening of 75-year-old patients fulfills these requirements in a way that few other groups do. Other groups may have similar stroke risk (i.e. CHA₂DS₂-VASc ≥ 2) e.g. 65-year-olds with diabetes or hypertension, but the expected AF prevalence will be lower. Seventy-five year-old patients have just reached the age when age alone is considered sufficient for OAC treatment by the current European guidelines on the management of AF.¹⁶ The 75-year-old age group is also representative of AF patients in Sweden where the median age in hospital-diagnosed AF is 76 years for men, and 81 years for women.¹⁰⁴ At the age of 75 years the remaining life expectancy in Sweden is 11.0 years for men, and 13.1 years for women according to the most recent report from Statistics Sweden.¹²⁸ A reason for not studying a random sample of elderly patients of different ages as done in paper I is to provide for a screening concept that could be repeated annually as an ongoing project if the screening should turn out to be successful. This is one of the criteria set up by the WHO and Socialstyrelsen (Table 3) for appraising the

appropriateness of screening. A random sample of elderly individuals would not suit that purpose.¹²⁸

A major screening study (STROKESTOP) was therefore launched in 2012 in which 25,000 Swedes aged 75 and 76 years were randomized either to participate in a 14-day screening program using 30-second handheld intermittent ECG recording to detect asymptomatic AF, or to act as control group¹⁴⁹. Inclusion in the study has now closed and a manuscript has been submitted. The results of this study will show the feasibility of this method for a national screening program, depending on: 1) costs of screening; 2) percentage of non-responders; 3) number of new AF patients that would have been detected without screening; 4) costs of OAC treatment; 5) stroke risk; 6) reduction of stroke risk because of medical treatment; 7) effect of a stroke on quality of life, risk of premature death; 8) costs of care after a stroke; 9) percentage of discovered patients that receive OAC treatment (Hälsoekonomisk utvärdering gällande primärpreventiv screening av förmaksflimmer med tum-EKG, 2014, TLV). The Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV) has done a cost-effectiveness study (Kunskapsunderlag: Hälsoekonomisk utvärdering gällande primärpreventiv screening av förmaksflimmer med tum-EKG, 2014, TLV) based on unpublished data from the STROKESTOP study.^{128, 129} Preliminary data from the STROKESTOP study showed a detection rate of 3% new AF. The report concluded that the advantages are great enough to justify costs for screening and that the studied primary preventive screening is cost-effective based on our present scientific knowledge. Costs for each added QALY were estimated at SEK 39,000 (€4200). In the STROKESTOP study the screened population, the invited non-responders, and the controls will be followed prospectively for 5 years after the inclusion of the first participant. The main endpoint of STROKESTOP is ischemic stroke. Secondary endpoints are: any thromboembolic event, intracranial bleeding, other major bleeding, death from any cause, and a composite of these. Furthermore, the authors will study whether OAC treatment is protective against AF-associated dementia.¹²⁸

Screening in specific groups at risk of AF and stroke

Routine screening in patients with an enlarged left atrium cannot be recommended at present. Designing a study screening patients with larger left atrial volumes e.g. ≥ 34 (moderately enlarged) or ≥ 40 ml/m² (severely enlarged) might give different results. A study designed to follow the development of AF burden and left atrial size over time in new paroxysmal AF patients could give us more clues regarding the relationship between AF and left atrial enlargement.

Data showing that most new AF patients, when screening in patients referred for cardiac ultrasound, come from Primary Care, support other studies indicating the need to screen Primary Care patients for AF. The usefulness of screening for AF regarding stroke prevention in Primary Care still has to be confirmed by larger randomized studies with hard end-points,

such as mortality and stroke incidence, before general recommendation on screening can be given. Hopefully the STROKESTOP study will give us some answers to this question.

Routine screening for AF in patients with sleep apnea can at present not be recommended as the study was not designed to answer that question. The studied population was too small to draw any conclusions related to the detection of previously unknown AF. To answer that question another study should be designed. In such a study the sample size is estimated at 579 patients plus 90 for potential loss, thus 669 patients to detect a significant difference of $p < 0.05$ with a power of 80% if the frequency of new AF is 1.5% among patients with sleep apnea compared with 0.5% in the general non-sleep apnea population at age 55.

Considering the high prevalence of AF in sleep apnea patients and the independent association of AF presence with age ≥ 60 years, central sleep apnea and diabetes, we would still suggest opportunistic screening of SA patients with an age over 60 years, with central sleep apnea and with diabetes. However, a general recommendation requires larger control studies.

Other future studies trying to identify suitable groups for AF screening could focus on other patient groups with conditions that have been associated with a higher AF prevalence, such as hypertension, symptomatic heart failure, mitral valve disease, cardiomyopathies, atrial septal defects, coronary artery disease, diabetes, athletes and chronic renal disease.

Investigating palpitation patients

Short intermittent ECG is much more effective than 24-hour Holter in detecting arrhythmias in patients with palpitations or dizziness/presyncope. Therefore 24-hour Holter should be phased out as the method of choice in these patients and be replaced by either the method used in our study, other similar methods, or methods using continuous registration during a longer time such as patch-based appliances. To create more awareness a case-description with the above recommendation as its conclusion has been published in the Swedish Journal of Medicine (Läkartidningen).¹⁵⁰ We are planning for an implementation study to increase the use of handheld short intermittent recordings as an alternative to 24-hour Holter in Primary Care. We are also planning for a study comparing the efficacy of 7-day Holter with a regime of short intermittent ECG recording during several weeks in cryptogenic stroke patients.

CONCLUSIONS

I. Opportunistic screening with intermittent handheld ECG registration over four weeks showed a detection rate of 3.8% of previously undiagnosed AF, in a population (n = 928) of out-of-hospital patients having at least one additional risk factor for stroke. This study shows very high compliance, suggesting that opportunistic screening using this method could be a feasible technique for detection of AF.

II. Short intermittent ECG recording, at regular time intervals and when having symptoms, during a four-week period, is more effective than routine 24-hour Holter ECG in detecting AF and PSVT in patients with palpitations. The fact that half of the AF episodes were asymptomatic implies that even event recording has its limitations in this patient category.

III. Patients with an enlarged left atrium (LA) did not have a higher prevalence of previously unknown paroxysmal AF compared with normal size LA patients. This study therefore does not support screening for silent AF in this particular group. While patients with early paroxysmal AF did not show any tendency to increased LA size, patients with persistent AF (duration >10 months) did. Our data thus support the hypothesis that early paroxysmal AF precedes LA enlargement and may be one of the factors causing LA enlargement.

IV. AF is common in sleep apnea patients, it occurs in 7.6% of sleep apnea patients and almost 15% of patients with sleep apnea ≥ 60 years. AF prevalence increases with the severity of sleep apnea. Independent risk factors for AF among patients being investigated for suspected obstructive sleep apnea include occurrence of central sleep apnea, age ≥ 60 years and diabetes mellitus.

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APPENDICES

APPENDIX A. CRF DATA

CRF Data collected in paper I.

All included patients	
Sex	male/female
Age	years
Health care center	name
Period of registration	date
Number of registrations	number
Congestive heart failure	yes/no
Hypertension	yes/no
Diabetes	yes/no
Earlier stroke/TIA	yes/no
Ischemic heart disease	yes/no
Sinus arrest	yes/no
AV-block II or III	yes/no
VT	yes/no
Frequent SVES	yes/no
Received pacemaker	yes/no
Detection of gastrointestinal bleeding	yes/no
AF patients	
Number of AF episodes	number
Duration of AF episodes	10 or <10 seconds
Time to first episode	days
Mean heart frequency during episode	number per minute
Time of episode	morning, evening, other
Symptoms during AF episode	yes/no
Symptoms without AF episode	yes/no
Anticoagulation	Warfarin, ASA, other
Other medication	Digoxin, Sotalol, Metoprolol, Tambocor
Cardioversion	yes/no

Appendices

CRF Data collected in paper II.

All included patients	
Sex	male/female
Age	years
Period of registration	date
Congestive heart failure	yes/no
Hypertension	yes/no
Diabetes	yes/no
Earlier stroke/TIA/TEE	yes/no
Ischemic heart disease	yes/no
Smoking	yes/no
Palpitations	yes/no
Number of palpitation episodes last year	number
Duration of episodes	minutes
Presyncope	yes/no
Perspiration	yes/no
Chest pain	yes/no
Fatigue	yes/no
Number of registrations	number
AF	yes/no
PSVT	yes/no
AV-block II or III	yes/no
Sinus arrest	yes/no
WCT	yes/no
Cardiac ultrasound	yes/no - data
Carotid Doppler	yes/no - data
Abnormal 12-lead ECG	yes/no - data
Arrhythmia patients	
Number of symptomatic registrations	number
AF/PSVT episodes with symptoms	% of total number AF events
Symptomatic registrations without AF/PSVT	% of total number symptomatic registrations
Time to arrhythmia detection	days

Appendices

CRF Data collected in paper III.

All included patients	
Sex	male/female
Age	years
Height	cm
Weight	kg
BMI	kg/m ²
BSA	m ²
Period of registration	date
Number of registrations	number
Cardiac ultrasound date	date
Home Health Care center	name
Referred by	Primary Care/Hospital clinic
Congestive heart failure	yes/no
Hypertension	yes/no
Diabetes	yes/no
Earlier stroke/TIA/TEE	yes/no
Vascular disease	yes/no
AF	yes/no
LA diameter	mm
LA volume	ml
Triage BNP	pg/ml
EF	%
LA strain rate	1/s
Valvular insufficiency	yes/no
Valvular stenosis	yes/no
Pulmonary hypertension	yes/no
Left ventricle dysfunction	yes/no
Beta-blocker	yes/no
Digitalis	yes/no
ACE/ARB	yes/no
(N)OAC	yes/no
Platelet inhibitor	yes/no
Diuretic	yes/no
Calcium blocker	yes/no
Anti-diabetic	yes/no
Anti-arrhythmic	yes/no
Thyroid hormone	yes/no
AF patients	
Number of AF episodes	number
Time to first episode	days
Mean heart frequency during episode	number per minute
Point of time of episode	morning, evening, other
Symptoms during AF episode	yes/no
Symptoms without AF episode	yes/no

Appendices

CRF Data collected in paper IV.

All included patients	
Sex	male/female
Age	years
Referred by	Primary Care/Hospital clinic
Period of registration	date
Number of registrations	number
Known AF	yes/no
New AF 12-lead ECG	yes/no
New AF handheld ECG	yes/no
Congestive heart failure	yes/no
Hypertension	yes/no
Diabetes	yes/no
Earlier stroke/TIA/TEE	yes/no
Ischemic heart disease	yes/no
Smoking	yes/no
Use of snus (moist oral snuff)	yes/no
Snoring	yes/no
Fatigue	yes/no
Apnea	yes/no
Other symptoms	yes/no - text
Beta-blocker	yes/no
Platelet inhibitor	yes/no
(N)OAC	yes/no
Blood pressure	mmHg
Height	cm
Weight	kg
BMI	kg/m ²
Epworth sleepiness scale	points
Abdominal circumference	cm
Neck circumference	cm
AHI	episodes/hour
OAHl	episodes/hour
CAHI	episodes/hour
ODI	episodes/hour
Mean saturation	%
Lowest saturation	%
Saturation < 90%	%
Mean apnea duration	seconds

APPENDIX B. Epworth Sleepiness Scale

The Epworth Sleepiness Scale

The Epworth Sleepiness Scale is widely used in the field of sleep medicine as a subjective measure of a patient's sleepiness. The test is a list of eight situations in which you rate your tendency to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing. When you finish the test, add up the values of your responses. Your total score is based on a scale of 0 to 24. The scale estimates whether you are experiencing excessive sleepiness that possibly requires medical attention.

How Sleepy Are You?

How likely are you to doze off or fall asleep in the following situations? You should rate your chances of dozing off, not just feeling tired. Even if you have not done some of these things recently try to determine how they would have affected you. For each situation, decide whether or not you would have:

- No chance of dozing = 0
- Slight chance of dozing = 1
- Moderate chance of dozing = 2
- High chance of dozing = 3

Write down the number corresponding to your choice in the right hand column. Total your score below.

Situation	Chance of Dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

Total Score = _____

Analyze your score

Interpretation

- 0-7:** It is unlikely that you are abnormally sleepy.
- 8-9:** You have an average amount of daytime sleepiness.
- 10-15:** You may be excessively sleepy depending on the situation. You may want to consider seeking medical attention.
- 16-24:** You are excessively sleepy and should consider seeking medical attention.

With kind permission of Dr. Murray Johns. Reference: Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep*, 1991; 14(6):540-5.