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DETECTION OF PAROXYSMAL ATRIAL FIBRILLATION WITH EMPHASIS ON INTERMITTENT ECG RECORDING

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To my beloved family Louise, Madeleine, Isabelle and our soon-to-be-born child



Karolinska Institutet

DETECTION OF PAROXYSMAL ATRIAL FIBRILLATION WITH EMPHASIS ON INTERMITTENT ECG RECORDING

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ABSTRACT

Atrial fibrillation (AF) is the most common sustained form of arrhythmia, affecting approximately 3 % of the adult population. AF may be symptomatic or asymptomatic. Asymptomatic paroxysmal atrial fibrillation (PAF) can be troublesome to diagnose, as most devices for arrhythmia detection provide only limited insight into heart rhythm. Regardless of the presentation of AF, it imposes the same risk of thromboembolic events.

The main purpose of these studies was to explore feasible methods for PAF detection. In **Study I** we evaluated the sensitivity and specificity of a handheld electrocardiographic (ECG) device by comparing concomitant 12-lead ECG registrations in 100 patients. Secondly, patients undergoing direct current (DC) cardioversion were asked to perform intermittent ECG recordings to investigate the ability to detect AF recurrence. Thirdly, 606 persons of the general public performed an ECG recording using the handheld device for feasibility assessment. Sensitivity and specificity of AF detection were 92% and 96 % respectively. Asymptomatic recurrence of AF after DC conversion occurred in 3/12 patients and was detected prior to standard follow-up. During screening, we detected previously undiagnosed AF in 1 % of the subjects.

In **Study II**, 22 patients with previously diagnosed PAF performed intermittent handheld ECG recordings, twice daily, for 30 days. Concomitantly they also performed a 24-hour continuous ECG registration. Using intermittent ECG recordings, 18 patients (82 %) were diagnosed with PAF episodes compared with 7 (32 %) using a continuous recording ($p=0.001$).

In **Study III**, 249 patients without known AF who had recently suffered a cryptogenic ischaemic stroke/transient ischemic attack (TIA) were recruited. The patients underwent intermittent handheld ECG recordings twice daily for 30 days and performed a 24-hours continuous ECG recording in order to determine what modality detected the most patients with undiagnosed PAF. The diagnosis of PAF was set in 17 patients (6.8 %) all aged ≥ 65 . Intermittent ECG recordings diagnosed 15 patients, continuous recordings 2 patients and only 3 patients were diagnosed by both methods.

In **Study IV** 174 patients, without known AF but with a recent ischemic stroke/TIA, underwent an echocardiographic examination using Tissue Doppler Imaging (TDI) to evaluate structural and functional parameters of the left ventricle and left atrium. PAF was diagnosed in 15 (8.6 %) patients. Patients with PAF had larger Left Atrial Volume Index (LAVI) (37.2 ± 6.7 vs. 31.6 ± 8.6 ml/m²) and lower intrinsic velocities (A') in atrial (5.7 ± 2.4 vs. 8.8 ± 3.8) and ventricular (5.9 ± 2.2 vs. 7.2 ± 1.6) septa and higher LAVI/A' indices in ventricular (7.9 ± 4.6 vs. 4.6 ± 2.0) and atrial (8.8 ± 3.8 vs. 5.7 ± 2.4) septa. Receiver operating characteristic curve (ROC) analysis to detect later occurrence of AF was performed. The area under the curve (AUC) for LAVI was 0.71 and 0.78 for LAVI/A' in atrial septum.

Conclusions

Intermittent handheld ECG recordings accurately diagnose episodes of AF. Using intermittent ECG recordings over an extended period of time we can detect more episodes of AF compared with shorter continuous recordings in patients with and without known AF. Thus, the method appears to be an alternative to other modalities for AF screening. Echocardiographic investigations of LAVI, left atrial systolic contraction velocities (A') and indices for these values may indicate which patients have underlying silent AF and might be used for identifying patients suitable for AF screening.

LIST OF PUBLICATIONS

The present thesis is based on the following studies, which will be referred to by their Roman numerals

- I. **Sobocinski Doliwa P**, Frykman V, Rosenqvist M.
Short-term ECG for out of hospital detection of silent atrial fibrillation episodes.
Scandinavian Cardiovascular Journal. 2009 jun; 43(3): 163-168
- II. **Sobocinski Doliwa P**, Rosenqvist M, Frykman V.
Paroxysmal atrial fibrillation with silent episodes; Intermittent versus continuous monitoring.
Scandinavian Cardiovascular Journal. 2012 jun; 46(3): 144- 8
- III. **Sobocinski Doliwa P**, Änggårdh Rooth E, Frykman V, von Arbin M, Wallén H, Rosenqvist M.
Improved screening of silent atrial fibrillation after ischaemic stroke.
Europace. 2012 aug; 14(8): 1112-6
- IV. Waldenhjort D, **Sobocinski Doliwa P**, Alam Mahbubul, Frykman V, Engdahl J, Rosenqvist M, Persson H.
Echocardiography detects unknown atrial fibrillation in patients with a transient ischaemic attack or stroke.
Submitted

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LIST OF ABBREVIATIONS

A	Late ventricular filling peak velocity
A'	Cardiac velocity during late ventricular filling
AF	Atrial Fibrillation
AUC	Area Under the Curve
DC	Direct Current
DT	Deceleration Time
E	Early ventricular filling peak velocity
E'	Cardiac velocity during early ventricular filling
ECG	Electrocardiogram/Electrocardiograph
EF	Ejection Fraction
IVRT	Isovolumic Relaxation Time
LAVI	Left Atrial Volume Index
LA	Left Atrium
LV	Left Ventricle
MPI	Myocardial Performance Index
OAC	Oral Anti Coagulation
PAC	Premature Atrial Complex
PAF	Paroxysmal Atrial Fibrillation
PVa	Peak Pulmonary Vein a-wave flow velocity, cm/s
PVd	Peak Pulmonary Vein flow velocity during diastole
PVs	Peak Pulmonary Vein flow velocity during systole
ROC	Receiver Operating Characteristics
SR	Sinus Rhythm
TDI	Tissue Doppler Imaging
TIA	Transient Ischaemic Attack

1. INTRODUCTION

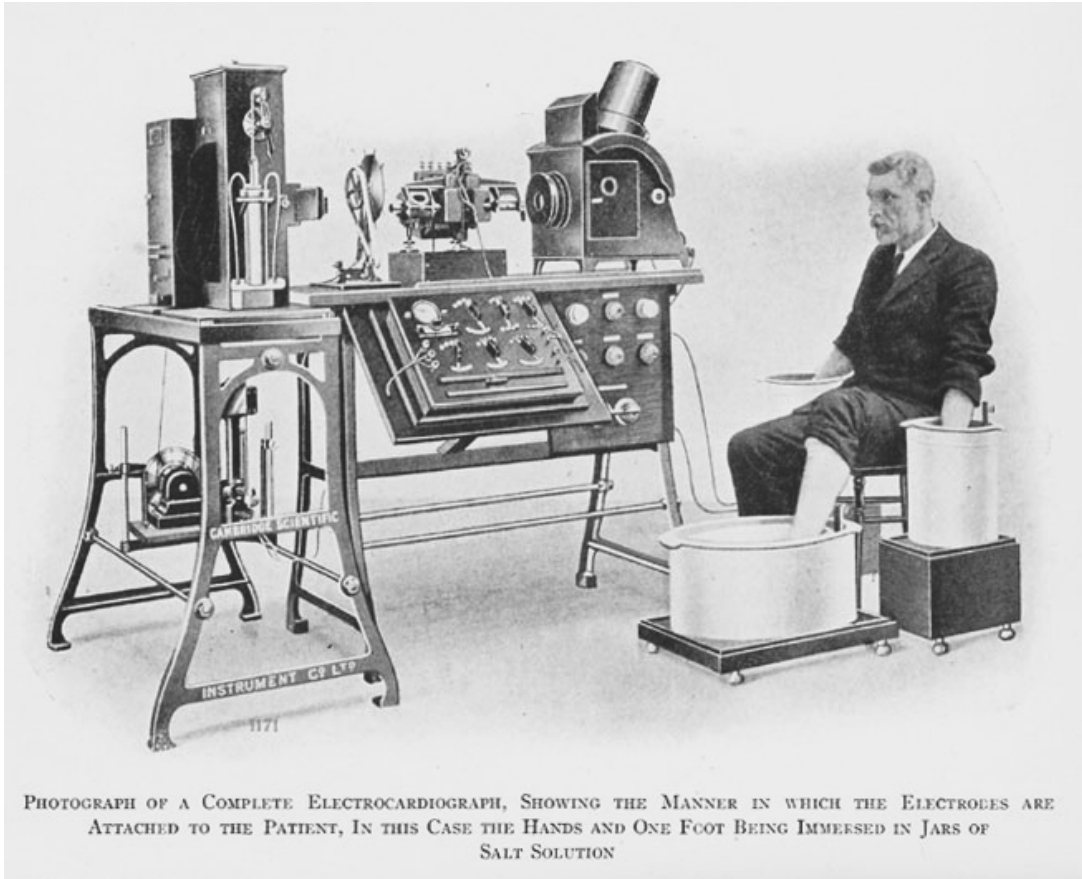
1.1 HISTORICAL PERSPECTIVES

The condition that is today known as Atrial Fibrillation (AF) can be traced back as far as 2000 B.C. in China where the Emperors physician described a condition of irregular chaotic pulse with poor prognosis in The Yellow Emperor's Classic of Internal Medicine (Huang Ti Nei Ching Su Wen). We then have to wait until the 17th century when William Harvey in 1628 described activation of the heart beginning in the atria and down into the ventricles. He also described the phenomenon of fibrillation of the auricles in animals.

At S.t Mary's Hospital in London, Augustus Waller performed the first electrocardiogram registration of a beating heart using the mercury capillary electrometer, in 1887. Waller's invention was improved and refined by Willem Einthoven, a professor of physiology in the Netherlands. His development of the electrometer would lead to the invention of a string galvanometer at the turn of the century that was able to perform electrocardiograms (ECGs). Due to the size and weight of the electrocardiograph (Figure 1) it would remain in his physiology laboratory some distance from the hospital and its patients. In order to use the electrocardiograph in clinical practice ECG registrations required transtelephonic transmission from the laboratory to the clinic. Findings and experiences from this were published in the paper "télécardiogram" in 1906.

With the invention of the electrocardiograph by Willem Einthoven, Sir Thomas Lewis was able to, a few years later (in 1909), to register the first ECG recording of AF (1, 2). Lewis would also become the first person to describe intermittent patterns of AF, which would later become known as paroxysmal atrial fibrillation (PAF).

Figure 1



Early ECG registration. www.creativecommons.org/licenses

1.2 MECHANISMS

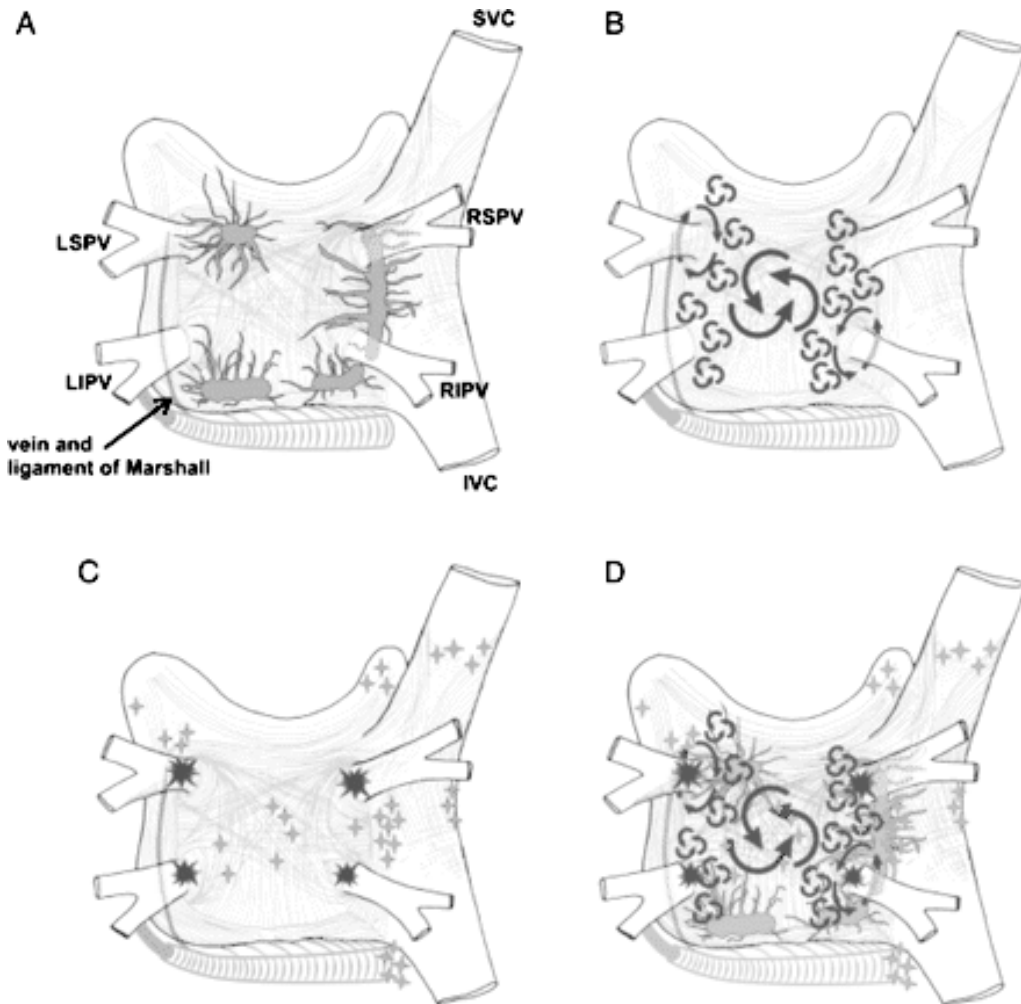
The mechanisms behind AF are to date not completely understood. There are three different mechanisms that are generally accepted, and at least in part play a role in the initiation and maintenance of AF. These are: multiple random propagating wavelets, focal electrical discharges and localized reentrant activity with fibrillatory conduction (3).

The theory of multiple random wavelets, described by Moe et al. (4) was the prevailing theory up until the eighties. The theory states that heterogeneity in the

atria, either due to structural changes or electrical imbalance, increases the risk of premature depolarization in cardiac myocytes of the atria, giving rise to small fibrillatory wavelets. Initiation of AF is a result of the occurrence of a critical number of such wavelets simultaneously propagating the span of the atrial myocardium in a random fashion. Maintenance is further dependent on factors such as refractory periods and excitable mass. Prolonged refractory periods and as a consequence decreased excitable mass lead to regularization of the wavelets with an increased chance of development into atrial flutter or termination of AF and conversion to sinus rhythm (SR).

In the mid-nineties the pioneering work of the Bordeaux group led by Haissaguere and colleagues proved that AF may stem from rapid firing foci, predominantly from the left atrium (5), (6). Cardiac muscle tissues reaching out into the pulmonary veins, so-called cardiac sleeves, have been the foci most implicated as regards the initiation of AF. However several other foci have also been described, such as the posterior wall of the left atrium and the superior vena cava. These foci are points of increased vulnerability to AF, due to heterogeneity in the tissue. The rapid firing foci give rise to so-called rotors, local circular reentries. These, in turn, break off as fibrillatory fragments that disperse through the atria (Figure 2). The subsequent AF leads to electrophysiological remodelling with altered cardiac myocyte ion channels within days. Electrophysiological remodelling promotes AF perpetuation and eventual structural remodelling. All electrophysiological and structural alterations (so-called AF substrate) promote further reentry tachycardia leading to AF.

Figure 2



Structure and Mechanisms of Atrial Fibrillation. Shown in Figure A, is a schematic drawing of the left and right atria as viewed from the posterior. The extension of muscular fibers onto the PVs can be appreciated. Shown in yellow are the five major left atrial autonomic ganglionic plexi (GP) and axons (superior left GP, inferior left GP, anterior right GP, inferior right GP, and Ligament of Marshall). Shown in blue is the coronary sinus which is enveloped by muscular fibers which have connections to the atria. Also shown in blue is the vein and ligament of Marshall which travels from the coronary sinus to the region between the left superior PV and the left atrial appendage.

Figure b, demonstrates the large and small reentrant wavelets that play a role in initiating and sustaining AF. Shown in Figure c, are the common locations of PV (red) and also the common sites of origin of non PV triggers (shown in green). Shown in Figure d, is a composite of the anatomic and arrhythmic mechanisms of AF. Adapted from Circulation, 28 Am J Cardiol, 733 Tex Heart Inst J.734. Europace. 2012 Apr; 14(4): 528-606

1.3 DEFINITION OF AF

According to current guidelines (7) AF is defined thus:

Surface ECG shows “absolutely” irregular RR intervals, i.e. RR intervals do not follow a repetitive pattern.

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 lead V1.

The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (> 300 bpm). (Figure 3)

Figure 3



ECG tracing of atrial fibrillation. www.creativecommons.org/licenses

An exception to the irregular pattern of AF seen on the surface ECGs is in the presence of complete atrioventricular block when the ventricular complexes become regular due to an ectopic escape rhythm. In addition to this definition it has also been recommended in these guidelines that the AF diagnosis should be

set by means of a 12-lead ECG or by an extended rhythm recording when a rhythm finding suggestive of AF is present for at least 30 seconds.

1.4 CLASSIFICATION OF AF

Atrial fibrillation can be classified according to duration and periodicity.

Paroxysmal AF is the term used when AF has a recurring pattern of at least two episodes where an AF episode terminates spontaneously within seven days.

Persistent AF is AF surpassing seven days or requiring, pharmacological or DC cardioversion for restoration of SR. In patients undergoing cardioversion within 48 hours AF is considered paroxysmal, whereas in patients, undergoing cardioversion later than 48 hours from AF start, AF is considered persistent (8). Persistent AF sustained for over one year is termed **longstanding AF** and when a decision has been taken to accept the AF and no further attempts are made to restore and maintain SR the AF is considered as **permanent**.

1.5 SYMPTOMATIC VS. ASYMPTOMATIC AF

Atrial fibrillation can be classified as symptomatic or asymptomatic. Common symptoms are: palpitations, shortness of breath and fatigue. Symptom severity is often related to the ventricular rate during AF (9) and is graded in existing guidelines (7) according to the EHRA (European Heart Rhythm Association) classification I-IV, where a higher number indicates more severe physical symptoms (Table 1). Treatment of AF may be steered to either heart rhythm or ventricular rate modification. Rate control implies decreasing the ventricular response during AF and rhythm control implies attempting to restore and maintain SR. The decision on what treatment strategy to choose depends which strategy provides the best symptom relief and is the most feasible from a patient-safety perspective.

Table 1

Classification of AF-related symptoms (EHRA score)	
EHRA class	Explanation
EHRA I	No symptoms
EHRA II	Mild symptoms; normal daily activity not affected
EHRA III	Severe symptoms; normal daily activity affected
EHRA IV	Disabling symptoms; normal daily activity discontinued

EHRA= European Heart Rhythm Association. Adapted from the European Society of Cardiology; Guidelines for the management of atrial fibrillation. European Heart Journal (2010) 31, 2369–2429

Both rate- and rhythm-control strategies are commonly implemented on the basis of findings in the AFFIRM (8) and RACE (10) trials, which compared rate versus rhythm control strategies and failed to show significant differences regarding overall mortality. It was further shown in the RACE II trial that a lenient rate control in patients with permanent AF was as effective as strict rate control (11) in terms of preventing cardiovascular morbidity and mortality. However, this view has been contested since further post-hoc analysis (12) has shown improved survival related to patient time in SR, suggesting prognostic benefits when choosing a rhythm control strategy. Adverse events related to the use of anti-arrhythmic drugs in the rhythm control arm have been proposed as the reason for the outcome of the AFFIRM and RACE studies.

Regarding prognosis in AF patients, however, prophylactic treatment for embolic complications by way of oral anti-coagulant (OAC) treatment plays a pivotal role. The risk of thromboembolic events, like ischaemic stroke, has been graded by the CHA₂DS₂-VASc scoring system, where the number of risk factors

is related to an exponential increase in stroke risk. The acronym encompasses: congestive heart failure, hypertension, age ≥ 75 y, diabetes, previous stroke/transient ischaemic attack (TIA), cardiovascular disease, age 65-74 y, and female gender. All these risk factors are awarded 1 point each except for age ≥ 75 and previous stroke/TIA, which are awarded 2 points each. In the presence of one or more of these risk factors, OAC or novel OAC drugs are strongly recommended according to contemporary guidelines (13, 14). Older studies have showed a yearly relative risk reduction for ischaemic stroke of approximately 60-70% using OAC and more recent trials of novel OAC have reported non inferior or superior results (15-17) compared with OAC in patients with AF.

Atrial fibrillation may also be completely asymptomatic. It has been estimated that as many as 32% of patients with AF are asymptomatic (18). Even in patients with previously diagnosed AF, paroxysms of AF may pass by unnoticed by the patients. Page et al concluded that only 1 out of 12 episodes of PAF were symptomatic to the patient (19). This pattern of poor correlation between symptoms and actual presence of AF has been shown in other studies as well (20, 21). As asymptomatic AF imposes the same risk of thromboembolic events as does symptomatic AF (22) the first sign of its presence may be an ischemic stroke, with potentially devastating effects. The pattern of PAF spans the whole spectrum from short infrequent episodes to longer, sometime daily episodes that are often asymptomatic, making it sometimes difficult to diagnose. Due to the wide range of periodicity of AF paroxysmal episodes, extended cardiac monitoring periods have proven beneficial in studies of patients who have recently suffered an ischaemic stroke or TIA, as more AF episodes are detected (23, 24). Screening studies for silent AF in the general public, using a handheld ECG recorder have detected 3.8% and 7.4% respectively during screening periods of up to one month (25, 26). In an ongoing screening study for PAF, persons aged 75 and 76 years are followed for two weeks using a handheld ECG recorder. Based on the ECG findings, persons are offered OAC treatment in order to determine whether or not such treatment of short AF episodes can decrease the number of new strokes in the future (27).

1.6 EPIDEMIOLOGY

Atrial fibrillation is predominantly a disease of the elderly with an increasing prevalence with increasing age (28). The highest prevalence is found in patients over the age of 80, with numbers close to 15% (29). The total prevalence in the general population is not fully known but estimates are rising. Previous estimates of AF prevalence have included approximately 1% (30) in the general population regardless of age. The numbers vary depending on AF classification investigated, demographics of populations examined and what criteria the investigators have had to designate a disturbance in the heart rhythm as AF. The above-mentioned approximation of AF prevalence for example, only took into account persistent AF. In recent studies these estimates have increased to close to 3.0% (29). These increases are a result of several factors such as improved AF detection, an aging population, taking into account all types of AF and extracting data not only from hospitals but also from outpatient clinics. The true number, however, will never be fully grasped as there are likely to be large numbers of people with silent undiagnosed AF. Both the patients and physicians may also misinterpret symptoms, as they may be mistaken for other more trivial disorders.

1.7 AF AND STROKE

Co-morbidities and potential causes of ischaemic stroke have been investigated for a long time and one of the main causative reasons for the development of ischaemic stroke has been considered to be arterial hypertension (31). In the 1950s more in-depth investigations were initiated concerning the relationship between stroke and potential risk factors. It was then further proposed that several conditions were more prevalent in ischaemic stroke patients compared with their controls, such as: hypertension, elevated cholesterol levels, diabetes mellitus, smoking, elevated haemoglobin levels, heart failure and ischaemic heart disease, although the causality was not completely understood (32) (33) (34). Some of these conditions are still valid and some have today been discarded. It was recognized that stroke patients to a higher degree had ECG changes of all types, such as: conduction abnormalities, and ST-T segment changes suggestive of left ventricular hypertrophy and coronary heart disease.

Arrhythmias, atrial fibrillation in particular, were also found to be more prevalent (35).

Early on, ECG registrations were not used as a diagnostic tool. Pathological ECG findings were, as stated above, fitted in to one category ranging from QT-prolongation to atrial fibrillation, explained by increased sympathetic activity and increased catecholamine levels as a consequence of an acute cerebrovascular accident.

It was not until the introduction of stroke intensive care units in the late 1960s with continuous 12-lead ECG monitoring during the initial 24 hours, that it was shown that not all ECG changes were permanent and present at admission, but had a rather dynamic and in part transient course (36). It was noted that AF was common in TIA and ischaemic stroke patients but the causal relationship was not fully grasped, as the prevailing theory was that cardiac arrhythmias caused transient or permanent hypoxia of the brain due to decreased cardiac output as consequence of either significant bradycardia or tachycardia, with resulting hypoperfusion of the brain (37) (38). The source of emboli was mainly considered to be prosthetic heart valves. Treatment for arrhythmias found upon admission was thus focused on ventricular rate control and sometimes pacemaker implantation in an attempt to improve cardiac output.

This would soon change with the publication of new Framingham data that introduced AF as a potential source of embolic stroke. It was proposed that persistent AF was a possible source of embolic stroke, where the duration of AF was correlated to the risk of stroke and, in the absence of rheumatic heart valve disease, that it was associated with a fivefold increase in stroke risk (39). A body of evidence was further gathered incriminating AF, in the absence of rheumatic heart valve disease, as a potential independent risk factor of the same standing as hypertension or cardiovascular disease. It was further shown that not only was persistent AF causative of stroke but also patients with sick sinus syndrome with intermittent episodes of AF (40). Additionally, patients treated for an acute stroke presenting with AF on the ECG at admission had an increased risk of recurrent stroke if not given OAC treatment (41). A new investigation of the

Framingham study disclosed that the risk of stroke was greatest at the beginning of AF onset, as most patients with stroke had newly diagnosed AF upon admission to the hospital (42). However, even at this point it was still estimated that AF was present in only approximately 10% of all stroke patients. It seems as if there was a trend at this point towards acceptance of the fact that AF is a risk factor of imminent ischaemic stroke regardless of whether it is chronic or paroxysmal (43) and that AF-related strokes may cause severe neurologic impairment (44) (45).

The introduction of extended ECG registrations beyond the initial 24- to 48-hour observational periods in stroke wards revealed an increased number of patients with transient paroxysmal AF episodes (46). Subsequent studies have further proven that PAF confers a risk of stroke as great as that of permanent AF (47). It has also become clear that sufferers of PAF do not necessarily have symptoms of all their paroxysms, a relatively large number of such episodes pass by undetected, recognized as asymptomatic or silent AF (19).

Subsequently, the question has been raised of whether such silent PAF episodes confer the same stroke risk as symptomatic an episode.

According to guidelines, AF, regardless of its clinical presentation, if detected in a patient who has suffered an ischaemic stroke or TIA, it clearly indicates further OAC treatment due to the high risk of a renewed stroke (14) .

1.8 DURATION OF PAF

Paroxysmal AF is unpredictable and the pattern of presentation is unique for each individual. Episodes of PAF may last from short bursts to episodes lasting for several days. It has also been proposed that paroxysms of AF may come in clusters over time (48). As a group, PAF patients have a similar risk of stroke, as do patients with permanent AF. Attempts have been made to determine whether PAF patients with a shorter time period in AF (AF burden) have the same risk of stroke as do those patients with a higher AF burden. Several studies have been performed in patients with implantable cardiac device and AF (22, 49, 50) in an attempt to answer this question. These studies have shown that a higher AF

burden increases the risk of stroke. Pooled data from some of the studies have shown a significantly increased risk with an AF burden surpassing one hour per day. However, the trend towards increased risk can already be observed with an AF burden of 5 minutes or more in these studies. This lower time requirement has also been observed in the ASSERT trial (51), which showed a 2.5-fold increased risk of ischaemic stroke with an AF burden with atrial high rate episodes of > 190 beats/minute surpassing 6 minutes. In some of the investigated patients, their AF episodes were observed several months into the screening period. Despite these apparently rare AF paroxysms these patients still presented with same risk of subsequent stroke as patients with persistent AF, which is interesting from a screening perspective. These results were based on patient groups that all had intracardiac devices. Whether these findings can be generalized to patients without such devices still has to be established. Do short episodes of less than 5 minutes on several occasions result in the same risk of stroke?

In support of the notion that even short disturbances of the SR confer an increased risk of stroke, the results of prospective studies indicate that even an increased amount of premature atrial complexes (PACs) or short episodes of supraventricular runs indicate a worsened prognosis (52) (53). Exemplifying this, Binici et al followed 678 healthy subjects aged between 55-75 years old followed for 6.3 years after a 48-hour continuous ECG registration. Patients with a number of PACs greater than 30 per hour, or with one or more episodes of supraventricular runs surpassing 20 consecutive beats had a worse prognosis in terms of AF, stroke and death.

1.9 AF SCREENING

The invention of the first Holter biotelemetry apparatus in 1947 by Norman Holter, (1914-1983), weighing approximately 40 kilograms, was the start of the telemedicine era (Figure 4). After some modification, technical advances and downsizing, the apparatus was ready for clinical and research use in 1962 (54). The benefit of ambulatory ECGs in the diagnosis of suspected cardiac symptoms such as paroxysmal arrhythmias and angina, and also for the evaluation of

medical treatment of such conditions, was quickly recognized (55). These indications are still today the most common reason for ambulatory ECG recordings in clinical practice.

Figure 4



Norman Holter wearing the first Holter ECG recorder (1947)

With the shift in theory that cardiac arrhythmias could cause ischaemic stroke or TIA, the notion of cardiac investigations by way of ECG recordings and cardiac echocardiography took shape (46).

It was soon realized that screening for arrhythmias for 24 hours does not diagnose all conditions, which is why monitoring time was extended to 48 hours, followed by the use of cardiac event recorders, able to monitor the cardiac rhythm for weeks. It was shown that increased monitoring time yielded more diagnoses (56). This led to further developments in screening methods, providing longer recording periods, and culminating in the development of implantable loop recorders that are inserted into the subcutaneous tissue, with a battery life of

approximately three years. Concomitant with the development of screening-only devices, methods were developed to interrogate intracardiac devices, i.e. pacemakers and implantable cardioverter defibrillators. Initially this was to monitor for lethal ventricular arrhythmias in patients with an advanced cardiac disease who might be in need of optimized medical treatment. The technique was refined over the years and is now finally able to show episodes of atrial arrhythmias.

1.10 AF AND ECHOCARDIOGRAPHY

1.10.1 Cardiac function

Cardiac function consists of two phases: systole and diastole. The left ventricular (LV) systole starts with the closure of the mitral valve. When the valve has closed the pressure rapidly increases due to ventricular contraction while the aortic valve is still closed, the so-called isovolumic contraction time (IVCT). Once the pressure in the LV surpasses the aortic pressure the aortic valve opens and the ejection phase begins. At this point the ventricle contracts and the blood volume is ejected into the aorta. As the blood volume decreases the LV pressure drops below the aortic pressure causing the closure of the aortic valve. Diastole now starts with the isovolumic relaxation time (IVRT) when the LV relaxes causing the LV pressure to further drop while the mitral valve is still closed. Once the LV pressure drops below the pressure of the left atrium (LA) the mitral valve opens and blood flows from the LA to the LV. Initially, during the early diastolic filling (E) of the LV, the flow is rapid due to pressure differences. There is a phase afterward which is called the diastasis when there is a very limited (sometimes nothing at all) flow of blood from the LA to LV due to almost equalization of pressure between these two chambers. This is followed by the late diastolic (A) filling which is an active phase due to LA contraction, during LA systole. In normal circumstances the rapid phase accounts for approximately 80 % of this volume. Once the LV volume has reached a certain level and the LV pressure increases concomitantly, the mitral valve closes once again.

1.10.2 AF and diastolic function

As stated earlier, the initiation and perpetuation of atrial fibrillation is enhanced by electrophysiological and structural changes in the heart that promotes electrical instability, due to changes in ion channels and an increase in excitable mass. Several studies have shown that the LA is of great prognostic importance in this regard. In particular, LA size and function have been found to exhibit a linear relationship in connection with adverse cardiovascular outcomes such as: AF, stroke, congestive heart failure and death (57-61).

Several methods have been developed for the evaluation of the LA. The most established and commonly used in the evaluation of the LA are: volume measurements of the LA, transmitral inflow velocities (into the LV) and the pulmonary vein inflow velocities (into the LA). According to guidelines (62), LA volumes are suggested to be measured using the biplane area length method indexed to the body surface area of the patient, i.e. left atrial volume index (LAVI). Velocity measurements, into the LV and the LA, as described above are performed using pulsed-wave Doppler that yields an indirect measure of the LA function but is preload dependent, why it is advisable to take several measurements into account when evaluating the cardiac diastolic function.

In recent years other new methods have developed in determining the LA function e.g. tissue Doppler imaging (TDI) (63-65) and strain/strain rate.

TDI provides a measurement of intrinsic myocardial velocities both during systole and diastole and is in contrast to pulsed-wave Doppler probably preload independent. It further provides a mean measurement of velocities compared to pulsed-wave Doppler that measures peak velocities, which may give overestimation of velocities. Due to normal aging, afterload increases due to an increased stiffness in the arterioles that causes an increased burden for the LV. This in turn causes impaired LV relaxation and compliance leading to diastolic dysfunction as observed in decreased early diastolic filling (E) and increased late diastolic transmitral filling (A) velocities (66). This reversed index of velocities can also be seen using TDI where E' velocities decrease and A' velocities

increase in the cardiac muscle (67). Diastolic dysfunction can also be seen in hypertension, obesity and diabetics amongst others.

As the LA wall is anatomically thin the increase in pressure usually causes dilation of the LA, which becomes a substrate for AF. Performing an echocardiographic examination while the patient is in AF it can be seen that the late diastolic A component, caused by the atrial contraction, of LV filling vanishes during AF, due to loss of atrial synchronic contraction. This leads to further deterioration of the diastolic function and promotes even further structural changes of the LA (68). The relationship between heart failure and AF is closely related where the AF prevalence increases with the severity of heart failure. The prevalence of AF in some heart failure patient groups has been found to be approximately 42 % (69) as compared to three percent in the population as a whole. It has sometimes been suggested that diastolic dysfunction is marker for AF.

After an episode of AF, reinstitution of SR (as shown on the ECG) might not show immediate recovery of mechanical function of the atrium as noticed by the absence of

A-wave at pulsed-wave Doppler, in many cases. This phenomenon is, sometimes referred to as “atrial stunning” (70, 71). Atrial systolic function might require days to weeks to regain its previous systolic function.

Owing to the close relationship between diastolic dysfunction, enlarged LA and AF, it seems plausible that diastolic dysfunction or enlarged LA may disclose patients who previously had PAF episodes or are likely to develop AF. An index for these parameters, LAVI/A' i.e. atrial volume index during atrial contraction, has also proved augmentation for this likelihood in previous retrospective studies (72-74).

2. AIMS

1. To investigate the feasibility and diagnostic yield of using a handheld ECG recorder for the detection of AF by way of intermittent ECG recordings.
2. To determine prospectively whether intermittent ECG recordings using a handheld ECG recorder for 30 days detects more patients with PAF episodes compared with a 24-hour continuous ECG recording in patients with diagnosed PAF.
3. To prospectively assess whether intermittent handheld ECG recordings, twice daily, for 30 days detects more patients with AF compared with a 24-hour continuous ECG recording in patients who have recently suffered an ischaemic stroke or TIA without a history of AF.
4. To prospectively evaluate the possibility of predicting, by echocardiography, later occurrence of PAF in patients who have recently suffered an ischaemic stroke or TIA without a history of AF.

3. MATERIALS AND METHODS

3.1 SUBJECTS

Study I

This study comprised three different parts, with three different groups of subjects.

The first part was aimed at evaluating the sensitivity and specificity of the handheld ECG recorder by investigating its ability to differentiate between AF and SR. In 2003, 100 AF patients regularly measuring their INR (international normalized ratio) values at the outpatient clinic for OAC prescription were consecutively enrolled in the study.

In the second part our objective was to explore the device in the patients' home environment. We therefore included consecutive patients (n= 12) at Södersjukhuset for one week. These patients had the diagnoses of symptomatic persistent AF and were scheduled for elective DC cardioversion. Their mean age was 64 years (range 43-87).

In the third part we aimed at exploring the ability of the handheld ECG to screen for AF in the general public. During the 2005 annual ESC (European Society of Cardiology) congress in Stockholm we invited the general public passing by to undergo handheld ECG registration in order to screen for the presence of AF.

Study II

To evaluate whether intermittent handheld ECG registrations over an extended period of time detect more patients with episodes of PAF, we enrolled 25 patients with previously diagnosed PAF from the Cardiology clinics at Södersjukhuset and Danderyd Hospital. Patients recruited from Södersjukhuset were from a previously (2002) composed registry (SCAF; Stockholm Cohort of Atrial Fibrillation). This registry contains all patients visiting Södersjukhuset in 2002 with the diagnoses of AF or atrial flutter according to the ICD (international classification of diseases) code. Consecutive medical records were investigated and patients with recent symptoms of PAF at least once every three

months were included.

Patients enrolled from Danderyd Hospital were from the arrhythmia centre, with pertinent ICD codes. In a similar fashion as above consecutive patients were enrolled on the basis of symptoms of PAF more than once every three months. For the final analysis of the material 3 patients were excluded due to progression from PAF to persistent AF.

Study III

With the objective of investigating the prevalence of unknown AF in patients who had recently suffered an ischaemic stroke or TIA, patients were recruited from Danderyd Hospital, Södersjukhuset and Halmstad Hospital. Altogether, 290 patients were recruited between 2007 and 2010. Inclusion criteria were clinical signs according to the National Institute of Health Stroke Scale (NIHSS) indicating ischaemic stroke or TIA and/or radiological signs in CT scans. Further criteria were inclusion within two weeks of the index event, and, based on patient interviews and scrutiny of past medical records, no previous AF. Patients diagnosed with AF during their hospital stay before inclusion into the study were excluded. Halfway through the inclusion period an amendment was added, i.e. a lower age limit of 70 years for inclusion of patients. This was a result of overrepresentation of younger patients. Exclusion criteria were previously diagnosed AF, intra-cerebral haemorrhage, dementia, inability to understand patient information, and chronic ventricular pacing in pacemaker patients, where evaluations of a patient's own underlying rhythm was not possible. In all, 41 patients were excluded as a result of compliance problems (n=29), misdiagnosis (n=7) and being erroneously included because of the age criterion that was later amended (n=5), leaving 249 patients eligible for final analysis.

Study IV

This was a sub-study of Study III, where 174 patients out of the previous cohort of 249 were consecutively enrolled (Table 2).

Table 2 Patient characteristics

	All	non AF	AF	p
Number of patients	174	159	15	
Age, years, mean (range)	74 (48 -91)	74 (48 -91)	75 (65 -84)	0.68
Gender, male	104 (60%)	98 (62%)	6 (40%)	0.10
Smokers	19 (11%)	18 (11%)	1 (7%)	0.58
Diabetes mellitus	29 (17%)	28 (18%)	1 (7%)	0.28
Congestive heart failure	7 (4%)	7 (4%)	0 (0%)	0.41
Previous stroke/TIA	39 (22%)	35 (22%)	4 (27%)	0.68
Ischaemic heart disease	41 (24%)	39 (25%)	2 (13%)	0.33
Hypertension	112 (64%)	103 (65%)	9 (60%)	0.71
Previous palpitations	26 (15%)	22 (14%)	4 (27%)	0.18

The aim was to explore the possibility of prospectively predicting the occurrence of previously unknown AF by echocardiography. These patients underwent an elaborate echocardiography examination including TDI. Inclusion criteria were as in Study III. Results concerning patients later diagnosed with PAF during the follow-up period were blinded to the investigator until final evaluation of the material was completed.

3.2 METHODS

Study I

For determination of sensitivity and specificity, 100 patients were recruited from Södersjukhuset outpatient clinic. These patients were asked to undergo standard 12-lead ECG immediately followed by a 10-second ECG registration using the handheld ECG recorder. Recordings from the 12-lead ECG and the handheld ECG recordings were then evaluated separately and blinded from each other. The results were then compared in order to assess the ability to correctly diagnose AF from SR using the handheld ECG.

In order to investigate the method of intermittent ECG recordings in the patient's home environment 12 patients with persistent AF, scheduled for elective DC cardioversion, were enrolled during one week. The patients were asked to perform 10-second ECG recordings in the mornings and evenings for 30 days, starting in the evening after successful DC cardioversion. The patients were also asked to perform recordings in cases of heart palpitation that they recognized as being AF episodes. In this way we would be able to distinguish between symptomatic and asymptomatic episodes of AF. Transmitted ECG recordings were diagnosed continuously during the study period. As the patients already had pre-planned doctors' visits the ECG findings did not further change their treatment.

In the third part of the study we aimed to evaluate the handheld ECG recorder as a mass-screening device. For this reason we chose to participate in the public event of the 2005 annual European Society of Cardiology congress. At this event members of the public were invited to test their blood pressure and give blood samples for evaluation of their lipid profiles. In this setting, for two full days there was also a possibility to make an ECG registration using the handheld device. In these two days 606 persons underwent ECG registration. No predefined restrictions regarding gender, age or previous medical history were implemented. The diagnosis was set immediately and patients diagnosed with AF not previously known to them were advised to schedule an appointment with their general practitioner for further action.

Study II

In this study we set out to investigate whether short intermittent handheld ECG recording over an extended time period detects more patients with episodes of AF compared with a shorter continuous ECG recording. In order to ensure a high number of AF episodes we enrolled 25 patients with an already set diagnosis of PAF with frequent symptoms. We therefore included patients who, according to medical records had symptoms at least once every three months. Enrolled patients were asked to perform 10-second ECG recordings mornings and evenings for thirty days, and, in addition symptom-triggered recordings in the case of arrhythmia symptoms. During the 30-day screening period the patients also underwent a 24-hour continuous Holter recording. The results of the two methods were thereafter compared to each other.

Study III

To investigate the prevalence of previously unknown AF in stroke or TIA patients, we enrolled patients from three Swedish hospitals. Patients fulfilling inclusion criteria and accepting participation in the study were included consecutively. Medical records were investigated in order to create a risk profile of the patient according to the CHADS₂ scoring system (Table 3). Inclusion was in general performed within 48 hours of admission to hospital but was in a few cases delayed as a result of admission during the weekend when enrolment was not performed.

Table 3. Patient characteristics at inclusion.

Parameter	All	Non AF	AF
Number of patients	249	232	17
Gender, male %	57	58	47
Age, years	72 (39-91)	72 (39-91)	75 (66-84)
Diabetes mellitus %	16	16	12
Congestive heart failure %	4	4	0
Previous stroke /TIA* %	25	25	35
Ischaemic heart disease %	20	20	12
Hypertension %	65	65	65
Previous palpitations %	15	13	35
Mean NIHSS**on admission	0.9 (0-10)	0.9 (0-10)	0.7 (0-3)
CHADS2 mean at study inclusion	3 (5-2)	3 (5-2)	3 (5-2)
Carotid duplex examination %	92	94	89
Pathological %	61	57	35
Significant stenosis (> 70 %) %	6	7	0
Complete carotid artery occlusion %	3	3	0
LVEF*** depression %	6	6	6
Left atrial enlargement %	13	13	24

** Before current ischaemic incident, ** National Institute of Health Stroke Scale, *** Left Ventricular Ejection Fraction*

Patients were asked to perform intermittent 10-second ECG recordings twice daily, starting immediately, for a period of 30 days. They were also instructed to perform recordings in case of heart palpitations. As soon as possible, but after the start of transmitting intermittent ECG recordings a 24-hour continuous Holter recording was started. During the hospital stay and or shortly after, additional investigations as carotid duplex and cardiac echocardiography were performed as clinically indicated. ECG registrations were evaluated continuously. If AF was detected the patient was contacted and an appointment was scheduled for further discussion regarding potential medical treatment alterations, i.e. conversion to OAC treatment. By examining the hours of the day when transmissions were made we were able to deduce whether a recording was either a scheduled one or one carried out because of heart palpitations.

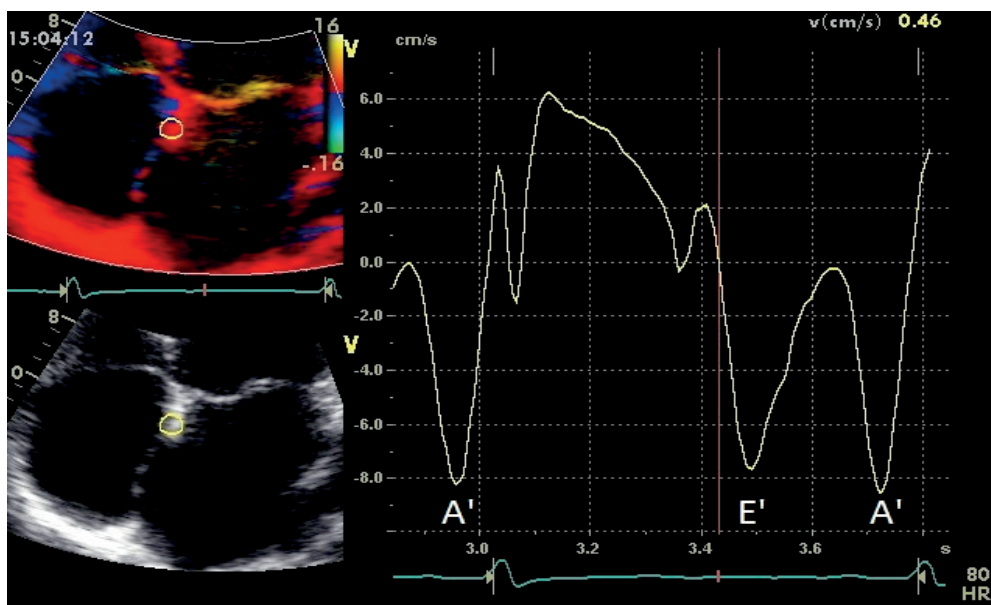
Study IV

The fourth study was a sub-study of Study III and instigated shortly after the start of the main study. Inclusion criteria were the same. Participating centres were the same as in Study III. In connection with hospital discharge the patients underwent an elaborate cardiac echocardiography examination, including TDI measurements, according to a predefined study protocol. The echocardiographic examinations were carried out at the individual enrolment centres and the results saved on a disc which was then sent to the core lab at Danderyd Hospital, where all the data were evaluated by the same person. A standard 2D examination was performed with the addition of TDI measurements including evaluation of diameters of the ventricles and atria, and ventricle wall diameters. In addition, evaluation of the cardiac valves and inflow velocities was performed by colour Doppler with continuous wave and pulsed wave Doppler as appropriate. Measurements were carried out in parasternal long-axis-, parasternal short-axis-, and apical and subcostal projections. Measurements of the LA volume were taken from both apical four- and two-chamber views and indexed for body surface area, using the biplane area-length method (LAVI). TDI measurements of the LV were taken from two- and four-chamber views. A high frame-rate was aimed for; 40-90 frames per second in 2D examinations and > 100 frames per

second in TDI and data was collected in three consecutive R-R intervals. TDI was used for evaluation of the LA systolic function during cardiac diastole. Intrinsic atrial septal cardiac velocity (A') was measured by placing the cursor over the atrial septum near the atrioventricular plane (Figure 5). Intrinsic cardiac velocities (A') for the ventricular septum were obtained by placing the cursor near the mitral annulus. Indices were then calculated: LAVI/ventricular A' and LAVI/atrial A' . In addition, measurements were taken for the myocardial performance index and other diastolic parameters: IVRT (Isovolumic relaxation time), DT (Deceleration time) E/A index and E/E' index.

All investigations were carried out using: GE/Vivid 7 Dimension/Vivid 7 PRO version 6.0x software. Information concerning the patients' ECG results was blinded to the investigator until all parameters had been fully calculated and evaluated. The echocardiography data and ECG results were then cross-referenced in order to determine whether some parameters diverged in comparison of the AF and non AF groups.

Figure 5



Colour coded TDI measurement of intrinsic atrial cardiac velocity (A')

3.3 STATISTICS

Study I was purely an explorative study aimed at determining whether it is feasible to use the handheld ECG device as a tool for diagnosing and screening for AF: thus no statistical methods were applied.

In both Study II and Study III we compared two methods against each other with the intention of showing the superiority of intermittent ECG recordings compared with 24-hour continuous recordings, and we therefore used McNemar's test for paired proportions. The criterion for significance (alpha) was 0.05 (two-tailed test). Power calculations were performed using Sample Power 2.0. Statistical analyses were performed using SPSS version 17 software.

For comparison between the two groups in Study IV, Students' *t*-test and the Mann-Whitney *U* tests were used, as appropriate. Chi-square test was used to test differences in proportions. Receiver operating characteristics (ROC) analyses were performed for variables of interest to assess the predictive ability to detect later occurrence of AF. For this study, analyses were performed with Statistica version 10 software.

3.4 ETHICS

All studies were performed in accordance with the declaration of Helsinki. Studies I and II were originally performed as quality control studies and therefore did not undergo a formal ethics approval. All participating patients in Studies I and II gave their oral consent.

Studies III and IV were both approved by the regional ethics committee and all patients gave written consent (reg. nos. 2007/386-31/2 and 2007/1376-32 respectively).

4. RESULTS

4.1 STUDY I. CAN INTERMITTENT HANDHELD ECG RECORDINGS DETECT AF?

The sensitivity and specificity of the handheld ECG device to correctly diagnose AF or SR were 92% and 96% respectively (Table 4). Out of 100 recordings, six were misdiagnosed by the handheld ECG device. Using the device four cases of atrial flutter were misdiagnosed as SR and in two cases SR was misdiagnosed as AF.

Table 4

	AF	Non AF	Sum
Positive finding	47	2	49
Negative finding	4	47	51
Sum	51	49	100

Table of findings yielding sensitivity (92%) and specificity (96 %)

Twelve patients planned for DC cardioversion were included. Of these, 11 were men. After successful cardioversion the patients were followed for 30 days, in which time they transmitted a total of 466 intermittent ECG registrations. Four patients had AF recurrence out of which three cases were asymptomatic. Patients diagnosed with AF recurrence were informed and asked to come to the outpatient clinic, where the diagnosis was confirmed by using 12-lead ECG. One patient discontinued the study prematurely as a result of inability to handle the device.

During two days of screening, 606 persons were investigated, yielding a mean time of 4 minutes per patient, including medical history regarding AF, registration for 10 seconds and information regarding the result. Persons of all ages were screened with the highest number in the age bracket of 60-79 y (45%).

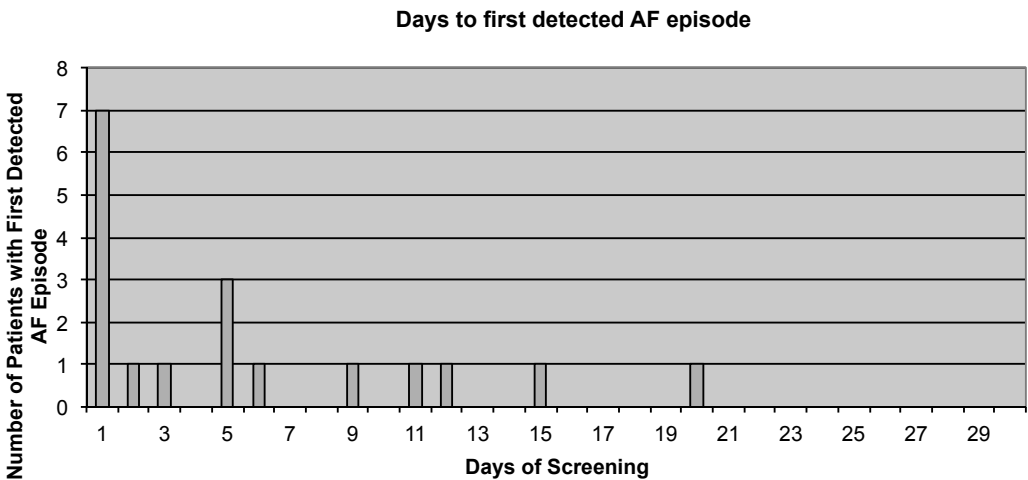
Twelve patients were diagnosed with AF (2%), out of which 6 cases (1%) were previously unknown.

4.2 STUDY II. DO INTERMITTENT ECG RECORDINGS OVER AN EXTENDED TIME PERIOD YIELD MORE AF DIAGNOSES COMPARED WITH SHORT CONTINUOUS ECG RECORDINGS?

Patients with a previous diagnosis of PAF (n=25) were enrolled consecutively from Danderyd Hospital and Södersjukhuset. When examining the recordings, three patients were excluded as a result of progression to persistent AF. The median age of the participating patients was 63 (range 46-77) and 73% (n=16) were male. Out of 1425 intermittent ECG recordings transmitted during the follow-up period, 98.2% were of sufficiently adequate quality for analysis. With intermittent handheld ECG recordings, 18 patients (82%) were diagnosed with episodes of PAF, compared with 7 patients (32%) in whom 24-hour continuous ECG recordings were carried out (p=0.001).

The median number of PAF registrations detected with continuous ECG recordings was one (range 1-6). With intermittent handheld ECG recordings a total of 250 episodes of AF were detected, distributed evenly over the day. Among these patients, 17 out of 18 were diagnosed within the first 15 days of the follow-up period (Figure 6).

Figure 6



Relationship between time and first detected AF episode using the handheld ECG device in patients with known PAF

In the 16 patients with SR during the 24-hour continuous ECG recordings, and displaying PAF episodes in intermittent ECG recordings, a median of 7 episodes (range 1-17) was detected. All patients diagnosed with PAF episodes in continuous 24-h recordings were also detected by means of intermittent ECG recordings.

4.3 STUDY III. IMPROVED SCREENING FOR SILENT ATRIAL FIBRILLATION AFTER ISCHAEMIC STROKE

A total of 249 patients with a mean NIHSS score of 0.9 (range 0-10) were enrolled in the study. The median age was 72 (range 39-91), with a median CHADS₂ score of 3 (2-5). The mean CHADS₂ score did not differ between the AF and the non AF groups. Out of the 249 patients AF was diagnosed in 17 (6.8%). Intermittent handheld ECG recordings detected PAF episodes in 15 patients. Three of these patients were also diagnosed with episodes of PAF by using continuous ECG recordings. An additional two patients were diagnosed with PAF by using continuous ECG recordings but not with intermittent

recordings (Table 5). There was statistical significance ($p=0.013$) in favour of intermittent ECG recordings for detection of AF.

Table 5

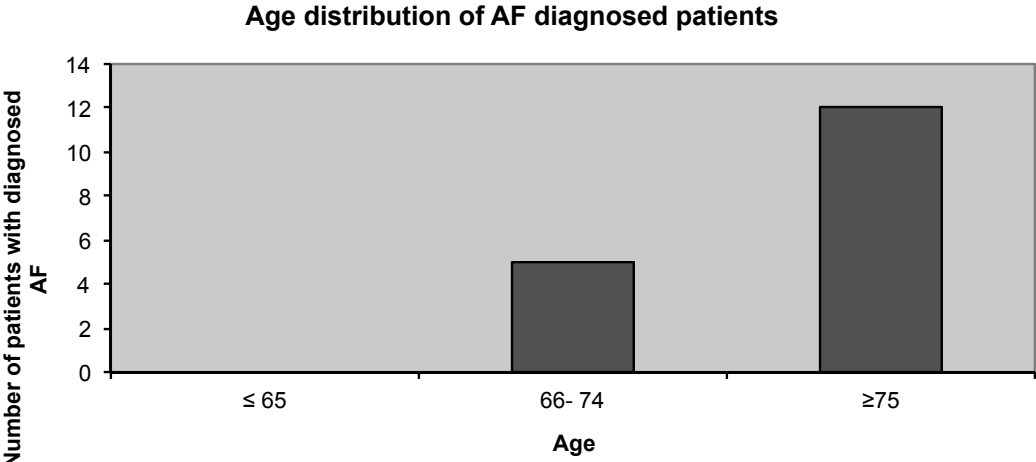
Method	Intermittent ECG positive	Intermittent ECG negative	Added results
24-h continuous ECG positive	3	2	5
24-h continuous ECG negative	12	232	244
Added results	15	234	Total: 249

AF diagnostics, comparing continuous and intermittent ECG screening.

No patients under the age of 65 were diagnosed with AF. The median age of the AF patients was slightly higher (75, range 66-84) than in the whole cohort (Figure 7).

In patients diagnosed with PAF, intermittent handheld ECG recordings showed a median number of 5 (range 1-22) recordings with AF. Only 22% of the recordings were symptom-activated recordings and most episodes (94%) of AF were diagnosed within the first 20 days of monitoring.

Figure 7



Age distribution of patients diagnosed with AF

4.4 STUDY IV. CAN ECHOCARDIOGRAPHY PREDICT LATER OCCURRENCE OF AF?

Out of the 249 enrolled patients in Study III, 174 made up the Study IV cohort, who, in addition to ECG recordings, also underwent an elaborate echocardiographic examination. The enrolled patients had a mean age of 74 and 40% were female. When cross-referencing to the ECG recording findings in Study III, 15 (8.6%) of the 174 patients were diagnosed with AF. Once all measurements and calculations in connection with the echocardiographic examinations were finalized, comparison between the AF and non AF groups was performed.

The AF group displayed a larger mean Left Atrial Volume Index (LAVI) compared with the non AF group (37.2 ± 6.7 vs. 31.6 ± 8.6 ml/m², $p=0.018$). Functionally, the AF group also showed lower intrinsic cardiac velocities (A') during atrial contraction in the ventricular septum (5.9 ± 2.2 vs. 7.2 ± 1.6 , $p=0.010$) and in the atrial septum (4.8 ± 1.4 vs. 5.9 ± 1.4 , $p=0.013$) compared with the non AF group. In addition, after calculating an index for LA volume and intrinsic septal velocities during atrial contraction (LAVI/A') further divergence was seen indicating an augmentation of the LAVI and A' values separately.

Measurements showed higher LAVI/A' values in ventricular (7.9 ± 4.6 vs. 4.6 ± 2.0 , $p=0.001$) and atrial (8.8 ± 3.8 vs. 5.7 ± 2.4 , $p=0.003$) septa (Table 6). Subsequently, ROC analyses for detection of PAF were performed; the AUC for LAVI was 0.71 and it was 0.78 for LAVI/A' in the atrial septum. Table 6

	All	non AF	AF	p
LAVI, ml/m²	32.0 (8.6)	31.6 (8.6)	37.2 (6.7)	0.018
A mitral inflow, cm/s	80.9 (26.2)	(81.4 (25.3)	76.2 (35.3)	0.500
A' ventricular septum, cm/s	7.1 (1.7)	7.2 (1.6)	5.9 (2.2)	0.010
A' atrial septum, cm/s	5.8 (1.4)	5.9 (1.4)	4.8 (1.4)	0.013
LAVI/A', ventricular septum	4.3 (3.2-5.8)	4.2 (3.2-5.5)	6.7 (5.0-8.7)	0.001
LAVI/A', atrial septum	5.3 (4.1-7.0)	5.1 (4.1-6.8)	8.5 (5.9-11.0)	0.003
LV E/E', mean	11.2 (3.8)	11.2 (3.9)	11.5 (2.9)	0.842
E/A, ratio	0.85 (1.17-1.53)	0.84 (0.72-1.08)	0.92 (0.81-1.37)	0.054
LV IVRT, ms	91 (25)	91 (25)	91 (25)	0.889
LV DT, ms	247 (24)	247 (25)	252 (24)	0.435
PVs/PVd	1.51 (0.41)	1.51 (0.42)	1.39 (0.35)	0.614
PVa, cm/s	32.0 (28.0-38.0)	32.0 (28.0-39.0)	30.5 (29.0-33.0)	0.483
LV mass index, g/m²	107 (22)	108 (23)	105 (22)	0.735
LV EF, %	62.7 (8.9)	62.5 (9.1)	64.5 (6.8)	0.473
LV MPI	0.51 (0.19)	0.51 (0.19)	0.54 (0.15)	0.553

Echocardiographic data

5. GENERAL DISCUSSION

It is well established that AF is an important risk factor for the development of stroke (39). It has also been established that PAF presents the same risk of stroke as does permanent AF (47). Some studies have further shown that even an increased number of PACs or short supraventricular runs increases the risk of AF and stroke (53), perhaps as markers of PAF already present. Along with this it is also known that increased screening periods for AF allows the detection of more episodes. The key to diagnosing AF seems to be an appreciation of its vast spectrum of presentation, ranging from symptomatic and chronic to asymptomatic with rare short paroxysms. When setting out to screen for AF one has to understand this and be aware of potential conditions that may increase the likelihood of the presence of AF.

5.1 SHOULD ALL STROKE AND TIA PATIENTS BE SCREENED FOR AF?

As the presence of AF has such a pivotal role as regards the further treatment of patients with an ischaemic stroke or TIA, it is essential to determine whether AF is present. In our material we detected an additional 6.8% of the stroke patients as having AF, a number that rose to 11.8% in the age bracket of 75 and older. According to the Swedish stroke registry RIKS STROKE it is estimated that approximately 30% of patients who present at the Emergency Rooms with a stroke or TIA have known AF (75). Adding this number to the findings in our study leads to the conclusion that more than one out of three stroke patients have AF. Based on our findings it is important to consider screening for occult AF in all ischaemic stroke patients without known AF. As AF and stroke are conditions where prevalence increases with age, there is a high likelihood of finding AF in stroke patients.

In our study no patients under the age of 65 were diagnosed with AF. This might therefore be proposed as a general lower age limit for AF screening in the

absence of other concomitant circumstances indicating AF. As the risk of thromboembolic events increases after a certain point of age, OAC treatment should be considered in all patients of ≥ 65 with AF, even in the absence of other risk factors according to CHA₂DS₂- VASc why this age limit seems appropriate.

Cardio embolic strokes in association with AF are often larger more severe strokes with more disabling symptoms. To a large extent the patients in our study presented only minor neurological deficits, as reflected by the low NIHSS points. This point underlines the importance of considering screening all patients, and using the CHA₂DS₂- VASc score for determining what patients to screen might be helpful. Even if AF did not cause the current stroke, detection might potentially prevent future more severe strokes caused by AF, especially as prophylactic OAC treatment may reduce the risk of stroke by approximately 60-70%.

The handheld ECG device has proven to be superior in detecting AF episodes in our studies. The method requires some technical proficiency on the patient's part, which is why some patients were not included, as their neurological deficits did not allow them to handle the device. It should be considered important to screen for AF from a primary prevention aspect, as we today have the medical means to substantially reduce the risk of future stroke.

There are today several screening programmes in Sweden for a variety of conditions (abdominal aortic aneurysm, breast cancer, colon cancer and cervical cancer), motivated by the fact that they are prevalent conditions in the general public associated with potential increases in morbidity, and mortality and there are effective treatments for them. According to figures from these screening programmes, abdominal aortic aneurysm and colon cancer, for example, have yielded findings of 1.4% and 0.2% respectively, requiring intervention (76, 77). In our study we found 6.8% in the whole cohort, which is a far higher number. The World Health Organization (WHO) has established criteria (Wilson-Jungner criteria) in order to determine what disease states are worth screening for from a socioeconomic perspective (Table 7) and AF fulfils all these criteria (27, 78). In

a recent and as of yet unpublished health-economic analysis, Levin et al showed that screening for AF in stroke patients, was directly cost-saving.

Table 7.

1. The condition should be an important health problem.
2. There should be a treatment for the condition.
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent stage of the disease.
5. There should be a test or examination for the condition.
6. The test should be acceptable to the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy on whom to treat.
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole
10. Case-finding should be a continuous process, not just a "once and for all" project.

The 1968 WHO Wilson-Jungner criteria for disease states that can be screened for

5.2 HOW SHOULD WE SCREEN FOR AF?

It is established that a longer duration of heart rhythm monitoring allows detection of more ECG findings that deviate from 12-lead ECG recordings.

Patients most often use external devices for cardiac monitoring, but the period of monitoring comes at a cost. Prolonged monitoring periods prolong the carrying of the device, which may be an obstacle in everyday life that may decrease patient compliance. Electrodes attached to the body may cause skin irritation. As it is probably not feasible or cost-effective to provide all patients with an implantable loop recorder with the ability to monitor the heart rhythm constantly over a significant time period, external devices should be chosen wisely. In patients with clinical suspicion of arrhythmia monitoring times can be chosen depending on the basis of the frequency of symptoms.

In patients without clinical symptoms of arrhythmia, the monitoring time to be chosen, yielding the highest detection rate, is less clear. At what point can one be fairly certain that a particular patient does not have underlying silent PAF?

In these studies we investigated the feasibility of using intermittent handheld ECG recordings over long time periods, which seems to be more efficient in diagnosing patients with unknown AF compared with the use of 24-h continuous recordings.

In patients who already had a diagnosis of PAF with relatively frequent symptoms, a substantial proportion of them had their first detected episode after a period up to two weeks of screening. Therefore, it seems as if this should be the minimum time duration for screening in any patient. In cases of frequent PACs or short supraventricular runs, these might be markers of AF, which is why it might be advisable to extend the monitoring period.

In contrast to continuous recordings we investigated a mode of screening for AF by way of intermittent handheld ECG recordings, twice daily with the addition of recordings made by the patients in the event of a perceived sensation of palpitations. This obviously leaves the investigator with the question of whether episodes of PAF in between recordings have been missed, and when a recording indicating AF is detected, what is the total duration of that episode? Is it longer than 30 seconds or shorter? One could speculate, however that the odds of catching a 10-second strip of a supraventricular arrhythmia that is shorter than 30

seconds have to be relatively small. According to AF guidelines, it is suggested that the diagnosis (either by way of 12-lead ECG or an extended heart rhythm recording) should be based on a pattern suggestive of AF for a duration of 30 seconds. This definition is based on an approximation rather than on scientific evidence. The recording time of a standard 12-lead ECG, however, lasts no more than 10-20 seconds. It therefore might be argued that concerning rhythm diagnostics, the handheld ECG device and 12-lead ECG are similar. If a patient performs 10-second handheld recordings twice daily for 30 days with no additional symptom-triggered recordings the monitored times equals 10 minutes out of 30 days (0.02% of the time). One could therefore assume that the likelihood of other rhythm disturbances such as PAF episodes is high.

Previous prospective studies have revealed that the mean duration of a PAF episode is approximately eight hours (79), which is why one could suggest that performing 2-3 registrations a day would present a fairly good chance of detecting such an episode. One could further speculate that a device that is not attached constantly may be less of an obstacle to the patient and thus improve compliance.

Most AF recordings in our studies were seen at planned recording times and not as additional symptom-triggered recordings. This indicated that only a minority of all AF episodes were symptomatic, a finding that is in accordance with those in previous studies. Choosing a strategy that encompasses both predefined times, determined by the investigator, complemented by those triggered by the patient's conceived sensations of arrhythmia is probably the most accurate method and yields the most reliable results.

Apart from the recommendation of opportunistic pulse palpation in patients over the age of 65, followed by a 12-lead ECG in cases of suspicion of AF (80, 81), there are currently no clear recommendations as regards or other methods of screening for silent AF. The method is probably of limited value, as the risk of under-detection is significant. In the recently published CRYSTAL AF study, patients with a cryptogenic stroke received an implanted loop recorder in order to evaluate the detection rate of silent PAF. Results at six months showed a PAF

prevalence of 8.9% compared with 1.4% in control subjects. The median number of days between randomization and detection of AF was 84.

There is also currently a lack of appropriate recommendations regarding whether or not there should be screening for AF, and if so how to screen for PAF after an ischaemic stroke. Neither is it clear what level of AF burden can be causative of a stroke, or whether repetitive short AF bursts have an additive or similar risk. It is therefore intriguing to seek other ways to pinpoint patients that have a high likelihood of PAF. By decreasing the number of patients aimed for screening, resources could be redirected to extended screening of a limited number of patients instead of random screening of all. Many ECG recordings reveal short episodes of irregular atrial activity that do not meet the 30-second criteria for AF, as suggested in the ESC guidelines. Having additional indications of the probability of underlying AF would potentially increase the yield of PAF screening.

5.3 WHAT PART DOES ECHOCARDIOGRAPHY PLAY IN SCREENING FOR AF?

In our study we evaluated the ability to prospectively predict the occurrence of AF within a short time span by echocardiography including TDI. Our results suggest that by measuring LA volume and LA functional indices discrepancies can be found between patients who later develop AF and those who do not irrespective of the presence of hypertension. In our cohort the AF group had larger LA volumes adjusted for Body surface area. Functionally we also saw that the AF group had slower intrinsic cardiac velocities in ventricular and atrial septa during atrial contraction. There were also significantly higher indices for LA volume and velocities (LAVI/A') for both ventricular and atrial septa. Thus, using these measurements, with certain cut-off values, with a high degree of accuracy we could rule out or rule in patients with AF detected in subsequent ECG screening. Perhaps the risks of stroke and TIA are not exclusively related to AF burden but can also be attributed to these diastolic parameters in the LA that enhance the likelihood of thrombus formation as none of the risk factors according to CHADS₂ scoring significantly differed between the groups.

Combining both an increased number of PACs and an abnormal LAVI/A' has retrospectively shown a high likelihood of PAF (74). As an echocardiographic examination is often performed in patients with stroke in order to exclude other sources of emboli, it could potentially be of value in identifying patients with an increased risk of AF. In such patients intensified ECG screening for AF could be recommended.

6. CONCLUSIONS

- Intermittent handheld ECG recording is a feasible method of screening for AF, providing high sensitivity and specificity for diagnosing AF and SR.
- Compared with continuous short-term ECG recordings, intermittent handheld brief ECG recordings over an extended time period detect more patients with episodes of PAF in patients previously diagnosed with PAF.
- In patients who have recently suffered an ischaemic stroke or TIA without previously known AF, intermittent ECG recording for 30 days detects more patients with PAF compared with continuous ECG recordings.
- An echocardiographic examination including TDI at discharge from hospital may prospectively predict later development of AF based on differences in LA volumes, diastolic parameters such as intrinsic cardiac velocities in the ventricular and atrial septum during atrial contraction and indices for these values (LAVI/A').

It therefore seems plausible that all patients with an increased likelihood of AF who suffer a stroke or TIA without previously known AF should have the benefit of an extended screening period for PAF. This likelihood may either be a result of increased age or other co-morbidities. In addition, an echocardiographic examination including TDI upon discharge from hospital with special focus on LA volume and LA indices for septal velocities during diastole may further provide guidance to decisions regarding OAC treatment and decisions concerning even more extended screening periods.

7. FUTURE PERSPECTIVES

Both permanent and paroxysmal AF reflect an increased risk of stroke regardless of symptoms. A remaining question is what AF burden finally causes an embolic stroke. Can primary screening of the general public prevent and decrease the number of strokes? Should primary screening be at a certain age or should it be based upon various comorbidities? In risk stratification, would the need of AF screening be limited to those who have conditions according to the CHA₂DS₂-VASc system, or should it further include patients with renal failure, thyroid disease and sleep apnoea for example, which have all been suggested as potential risk factors of AF?

As the prevalence of AF increase with age, the optimal screening period and optimal intervals of such screening must be established. There is today the ability to monitor heart rhythm for approximately three years by using implantable loop recorders (ILR) but this method has a high upfront cost and AF affects only a minority of the general public. The costs to society for each of the 30 000 Swedish individuals who suffer an ischaemic stroke each year, on the other hand are immense, apart from decreased quality of life, which is why the prevention of AF-related stroke is pivotal (75). Dependent on these two aspects it is important to determine what method for primary prevention AF screening is the most cost-effective.

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9. SVENSK SAMMANFATTNING

Förmaksflimmer (FF) är den vanligaste ihållande rubbningen av hjärtats rytm och uppskattas drabba cirka 3 % av befolkningen. Den anses i vissa fall vara en progressiv sjukdom. Det innebär att den inledningsvis uppträder under kortare perioder för att med tiden återkomma allt oftare och slutligen kan sjukdomstillståndet vara permanent. FF kan orsaka nedsatt ork, hjärklappning och bröstsmärta men kan likväl förekomma helt utan symtom. Oavsett symtombild medför FF en ökad risk för stroke. Det finns idag effektiv läkemedelsbehandling för att förebygga stroke varför det är viktigt att hitta och diagnostisera personer med FF för att minska stroke-risken. Hos personer med glesa FF-perioder utan symtom kan diagnosen dock vara svår att konstatera då metoder för EKG-övervakning endast ger en begränsad insyn i hjärtats rytm. En idag vanlig metod för att upptäcka FF är en kontinuerlig registrering av patientens hjärtrytm under ett dygn.

Syftet med studierna har varit att utvärdera en alternativ metod, Tum-EKG, för att upptäcka förmaksflimmer. Denna metod möjliggör korta EKG-registreringar med hjälp av tummarna.

Vi har i tre olika studier utvärderat den aktuella metoden. För att avgöra metodens diagnostiska tillförlitlighet jämfördes den i vår första studie mot standard-EKG avseende förmågan att diagnostisera FF och normal rytm. Metodens förmåga att upptäcka FF utvärderades genom screening av allmänheten samt hos en grupp patienter som genomgått en elkonvertering för sitt symtomatiska FF. Vi kunde konstatera en god diagnostisk tillförlitlighet samt goda egenskaper att upptäcka FF med hjälp av metoden.

Vidare jämförde vi metoden med kontinuerligt EKG under 24 timmar i syfte att utvärdera vilken metod som uppvisar flest patienter med FF-episoder. Under 30 dagar gjordes korta Tum-EKG-registreringar två gånger dagligen samt vid symtom av hjärtrymrubbning. Registreringarna jämfördes med ett dygns kontinuerlig EKG-registrering under samma period. Detta gjordes i två studier: hos patienter med tidigare diagnostiserat FF samt hos patienter som nyligen

drabbats av stroke, utan tidigare känt FF. Som förväntat hittades fler FF-episoder vid kontroller av EKG-rytmen under 30 dagar med hjälp av Tum-EKG-registreringar än vid kontinuerliga EKG-registreringar under 24 timmar.

I vår fjärde studie undersökte vi en del av patienterna som drabbats av stroke utan tidigare känt FF. Genom att i samband med utskrivning av patienten från sjukhuset genomföra en ultraljudundersökning av hjärtat och analysera storleken på hjärtats hålrum samt beräkningar av hjärtmuskelnns hastigheter gavs indikationer på vilka patienter som hade en förhöjd risk för FF senare under uppföljningsperioden.

Sammanfattningsvis har studierna visat att metoden med korta EKG-registreringar under 30 dagar har god diagnostisk tillförlitlighet och uppvisat god förmåga att diagnostisera FF-episoder hos både patienter med och utan känt FF. Anledningen torde vara att en förlängd period med kortare tum-EKG-kontroller av hjärtrytmen, istället för en kortare men kontinuerlig EKG-registrering under 24 timmar, ökar chansen att hitta FF-episoder. Vi har vidare kunnat se möjligheten att, genom bedömning av hjärtats struktur och funktion, bedöma sannolikheten för senare förekomst av FF.

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