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Implications of Brief Episodes of Atrial Fibrillation (Micro-AF)

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IMPLICATIONS OF BRIEF EPISODES OF ATRIAL FIBRILLATION (MICRO-AF)

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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"Two chambers hath the heart.

There dwelling,

Live Joy and Pain apart."

-Hermann Neumann, German poet, 1808-1875

In honour of my parents Ann-Sofi Ahlbom and Anders Fredriksson, for teaching me how to strive through the pain of tired eyes staring at textbooks during late nights before an exam and the joys of deciphering the secrets of both books and the heart.

ABSTRACT

INTRODUCTION

Atrial fibrillation (AF) is the most common clinically relevant arrhythmia. It is diagnosed using an electrocardiogram (ECG) and defined as an irregular heart rhythm without p-waves lasting for at least 30 seconds. This 30-second time criterion is based solely on expert consensus. AF is associated with a five-fold increase in stroke risk but with use of stroke preventive oral anticoagulation treatment, the risk can be reduced by at least two thirds. Connections between supraventricular activity, AF and stroke have been identified in register studies. Still, there are no studies evaluating the risks associated with episodes of AF-like activity with duration shorter than 30 seconds, termed micro-AF. One can assume that micro-AF is associated with AF, but there are no guidelines for clinicians on how to investigate or treat individuals with these findings.

The aims of this thesis are: 1) to evaluate if individuals with micro-AF have a higher risk of subsequent AF and thus would benefit from extended screening and follow-up; 2) to study the prevalence of micro-AF in an elderly population; 3) to postulate the time span from micro-AF to AF; 4) to assess if micro-AF burden predict development of AF; 5) to identify which investigation is the most suitable to detect AF in an elderly, high-risk population by comparing intermittent ECG and continuous event-recording; 6) finally, the thesis aspires to gain a larger perspective by comparing the risks associated with micro-AF to the risk increase in individuals with other types of excessive supraventricular activity.

METHODS AND RESULTS

The participants in study I were identified from STROKESTOP I, a population-based mass-screening study for AF. In STROKESTOP I individuals aged 75- and 76-years recorded intermittent ECGs for 30 seconds, twice daily for two weeks. Participants free from AF but in whom micro-AF was detected were followed-up. In study I micro-AF was defined as abrupt onset episodes of irregular heart rhythm, ≥4 consecutive supraventricular beats and absence of p-waves lasting for less than 30 seconds. Participants free from both micro-AF and AF acted as a control group. After 2.3 years both groups were invited to repeat AF screening using intermittent ECG for 30 seconds twice daily in parallel with continuous event-recording for two weeks. AF was found in 50% (n=27/54) of participants in the micro-AF group compared to 10% (n=5/48) in the control group, $p<0.001$. One hundred percent of the AF cases detected during repeat screening were found by the continuous event-recorder and of those, intermittent ECG detected 40%.

In study II, participants were identified from the STROKESTOP II study – similarly to STROKESTOP I, a mass-screening study for AF. In contrast only participants with N-terminal pro b-type natriuretic peptides (NT-proBNP) levels ≥125 ng/L were asked to perform intermittent ECG four times daily for two weeks. Participants free from AF but with micro-AF during intermittent recordings were invited to additional extended screening using continuous event-recording for two weeks. A tachycardia criterion was added to the micro-AF definition, and the duration was prolonged to ≥5 consecutive beats (the same definition was also used in study IV). A control group was screened using both ECG modalities simultaneously in STROKESTOP II. Continuous event-recording detected AF in 13% (n=26/196) in the micro-AF group and 3% (n=7/250) in the control group, p <0.001.

The group performing intermittent ECGs and continuous event-recording in parallel during STROKESTOP II were also invited to participate in study III. The participants were asked to fill out a questionnaire comparing ease of use and compliance to the two ECG modalities; the intermittent ECG, a Zenicor II device and the continuous event-recording, an R-Test 4 device from Novacor. Continuous event-recording detected new AF in 6% (n=15/269) and intermittent ECG in 2% (n=5/269), p=0.002. Both devices were well tolerated, but intermittent ECG was graded "very easy to use" whereas continuous event-recording was graded "easy to use", p<0.001.

Study I included parts of the participants with micro-AF in STROKESTOP I. In study IV an automated algorithm was used to identify all participants with micro-AF and other supraventricular arrhythmias in the STROKESTOP I database. All ECGs identified by the algorithm were also manually assessed. Participants were followed up using three-year data from National Swedish Health registers. Supraventricular tachycardias were associated with an increased risk of AF compared to excessive supraventricular ectopic beats. Participants with supraventricular tachycardias with AF characteristics, micro-AF, n= 97 (1,6%), were shown to have a higher risk of AF than participants with other supraventricular arrhythmias (hazard ratio 4,3; 95% confidence interval 2,7-6,8). They also had an increased risk of death (hazard ratio 2,0; 95% confidence interval 1,1-3,8).

CONCLUSION

Extensive supraventricular ectopy, including frequent isolated supraventricular ectopic beats and supraventricular tachycardias, is common and associated with AF development in elderly people. Individuals with supraventricular tachycardias with AF characteristics – termed micro-AF – showed the highest risk of a future AF as well as an increased risk of death. Micro-AF also seems to be associated with an increased risk of already existing undetected AF. The risk of having AF detected by screening seems to increase with time in individuals with micro-AF, indicating a possibly

progressive disease in the atria. We found no evidence that micro-AF burden affects AF development. Extended and repeat screening could be recommended for the elderly population with micro-AF as detection of AF in the majority of cases would lead to initiation of stroke preventive oral anticoagulant treatment. Intermittent ECG is well tolerated as a screening method in an elderly population, but continuous event-recording for two weeks detects three-times as many new cases of AF and is therefore a preferable screening method.

LIST OF SCIENTIFIC PAPERS

The thesis is based on the following studies, referred to by their Roman numerals

I.   **Fredriksson, T**, Frykman, V, Friberg, L, Al-Khalili, F, Engdahl, J, Svennberg, E

        Usefulness of Short-Lasting Episodes of Supraventricular Arrhythmia (Micro-Atrial Fibrillation) as a Risk Factor for Atrial Fibrillation.

        The American Journal of Cardiology, 2018, Oct 1; 122(7):1179-1184

II.   **Fredriksson, T**, Kemp Gudmundsdottir, K, Frykman, V, Friberg, L, Al-Khalili, F, Engdahl, J, Svennberg, E

        Brief episodes of rapid irregular atrial activity (micro-AF) are a risk marker for atrial fibrillation: A prospective cohort study.

        BMC Cardiovascular Disorders, 2020 Apr 10;20(1):167. doi: 10.1186/s12872-020-01453-w

III.   **Fredriksson, T**, Kemp Gudmundsdottir, K, Frykman, V, Friberg, L, Al-Khalili, F, Engdahl, J, Svennberg, E

        Intermittent vs continuous electrocardiogram event recording for detection of atrial fibrillation-Compliance and ease of use in an ambulatory elderly population.

        Clinical Cardiology, 2020 Jan 9. doi: 10.1002/clc.23323

IV.   **Fredriksson, T**, Stridh, M, Friberg, L, Svennberg, E

        Prognostic implications of supraventricular arrhythmias - from ectopy to micro-AF.

        Submitted

CONTENTS

LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
AHRE	Atrial High-Rate Episodes
BMI	Body Mass Index
NT-proBNP	N-terminal pro b-type natriuretic peptides
CI	Confidence Interval
CRT-D	Cardiac resynchronization therapy with defibrillator
ECG	Electrocardiogram
ESVEA	Excessive supraventricular activity
ESC	European Society of Cardiology
HR	Hazard Ratio
ICD	Implantable cardioverter defibrillator
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile Range
OAC	Oral Anti-Coagulation
Micro-AF	Episode of atrial fibrillation-like activity lasting for <30 seconds
PPM	Permanent pacemaker
SVEB	Supraventricular Ectopic Beat
SVT	Supraventricular Tachycardia
TIA	Transient Ischaemic Attack

PREFACE

The guidelines from the European Society of Cardiology define atrial fibrillation as an irregular heart rhythm with absence of p-waves lasting for at least 30 seconds. I recall a classmate raising her hand during a lecture at university asking why an arrhythmia had to last for 30 seconds to be classified as atrial fibrillation. We were told that changes in the movement patterns of the atrium during a longer time period lead to stasis and risk of thrombus formation. What was never made clear to us though was that the choice of a 30-second duration for the definition was completely arbitrary. During my last semester of medical studies, I came in to contact with Emma Svennberg, who at the time was working with STROKESTOP I, a mass-screening study for atrial fibrillation in 75- and 76-year olds using intermittent ECG. She had noticed that many of the participants had episodes that seemed similar to atrial fibrillation, but with a duration shorter than 30 seconds. They had no indication for oral anticoagulation, but would they benefit from follow-up?

This is where I entered the stage. I was just starting my PhD studies and was already focused on micro-atrial fibrillation. As I began pouring over the literature, I realized that an association between supraventricular ectopic beats, supraventricular tachycardia and atrial fibrillation had been seen in several register studies. Individuals with these arrhythmias were also shown to have an increased risk of stroke. Still there were no guidelines regarding follow-up and treatment of this group. The absence of guidelines could be at least partly explained by the long follow-up periods before atrial fibrillation was diagnosed in the register studies and the fact that the increased risk of stroke could be due to undiagnosed atrial fibrillation. I began asking myself if atrial thrombus formation could appear during short arrhythmia episodes, as I knew that atrial fibrillation patients had an increased risk of stroke even during long arrhythmia free periods. When I participated in a conference of the European Society of Cardiology in Rome during 2016, I got the chance to talk to some senior colleagues during a coffee break. That was when my eyes were opened to the theory of atrial myopathy that can both be prothrombotic in itself but also cause disturbances in the electrical signalling of the heart. Shorter arrhythmia episodes, like micro-atrial fibrillation, could be potential signs of atrial myopathy and therefore associated with an increased risk of stroke.

This thesis is an effort to establish the risks and clinical implications of short episodes of atrial fibrillation-like activity, i.e. micro-atrial fibrillation.

1   INTRODUCTION

1.1   Prevalence of atrial fibrillation

Atrial fibrillation (AF) is the most common clinically relevant cardiac arrhythmia in the adult population. The prevalence of clinically diagnosed AF is approximately 3% in the population >18 years of age (1-3). The prevalence increases with age and is slightly higher in men than in women per age strata (1, 4).

By 2010 about 30% of the total population in the European Union was ≥55 years old, a number expected to increase to 41.1 % by 2060 (5). This demographic shift in combination with a higher prevalence of AF in older populations give an estimated AF prevalence set to double within a 50-year period (5, 6). The expected lifetime risk of developing AF for middle aged men and women living in Europe and the U.S. today is approximately 25% (3, 4, 7).

The true prevalence of AF is probably underestimated in other parts of the world due to lack of epidemiological data, and this underestimation may also be true in Europe and the U.S. (8). AF can be asymptomatic and paroxysmal and could therefore remain undiagnosed. By screening a population of 75- and 76-year olds in Sweden, the AF prevalence increased from 9.3% before to 12.3% after screening (9).

Hence, an increase in AF prevalence may be both due to better detection of AF in asymptomatic patients (9-11), an ageing population and changes in AF-related co-morbidities (12).

1.2   Risk factors for atrial fibrillation

AF is commonly a multifactorial disease, and a single predisposing condition can be difficult to ascertain.

The European Society of Cardiology (ESC) has summarised the risk factors for AF. Early-onset AF is believed to have a strong genetic component. About one third of patients diagnosed with AF carry genetic variants predisposing for AF, although the increased risk of developing AF in these individuals is mild to moderate. In addition, simply being male is associated with AF. The diseases associated with an increased risk of developing AF are; diabetes mellitus, hypertension, valvular disease, heart failure, myocardial infarction, obstructive sleep apnoea, chronic obstructive pulmonary disease, obesity, renal failure and thyroid disease, (see figure 1). Also, lifestyle factors such as smoking, high alcohol consumption, but also both physical inactivity and extensive physical activity predispose for AF development (13, 14). Except from age, sex and genetics, many of these risk factors are potentially reversible. Hence, primary and secondary prevention for AF may be of interest (14).
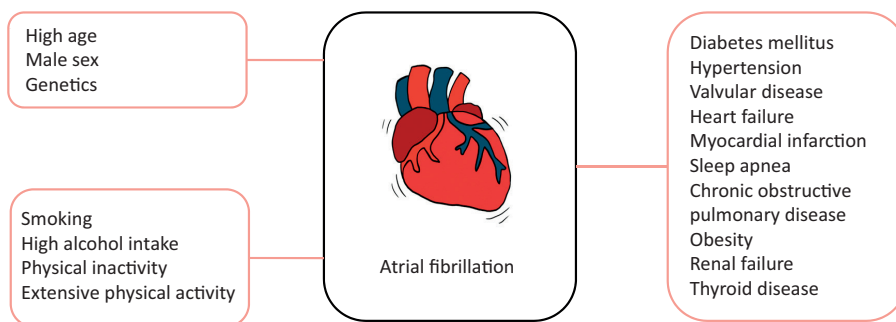
Figure 1. Risk factors for atrial fibrillation

1.3   Diagnostic criteria for atrial fibrillation

The diagnostic criteria for AF according to ESC guidelines include the following ECG patterns: absolute irregular rate-to-rate intervals, absence of normal p-waves and a duration of at least 30 seconds. The 30-second rule is due to accepted convention. The diagnosis of AF is independent of symptomatology (13).

During AF, atrial activity might be seen on the ECG, but the atrial complexes have a different configuration and a there is a variance in distance between the different atrial complexes. The atrial frequency during AF is >300 per minute (15) and cannot be assessed by a standard ECG recording.

1.4   Classification of atrial fibrillation

Based on presentation, duration and type of termination AF is classified into five different groups: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent (13). AF commonly progresses from short and infrequent episodes to more permanent forms over time, but the progression to permanent forms of AF is slower in young and healthy individuals (16).

- *First diagnosed AF* – when AF is first diagnosed in a patient with no prior diagnosis of AF.

- *Paroxysmal AF* – when AF terminates within seven days.

- *Persistent AF* – when an episode lasts for more than 7 days or if cardioversion is needed to restore sinus rhythm after ≥7 days.

- *Long-standing persistent AF* – when AF lasts for more than one year, but the aim is to regain sinus rhythm.

- *Permanent AF* – when the arrhythmia is life-lasting and is accepted by the physician and patient, who receives no rhythm control treatment (13).

1.5 Pathophysiology of atrial fibrillation

During normal sinus rhythm, the sinus node starts the electric signalling leading to progressive activation of the whole myocardium. The initiation of AF instead starts in one or several ectopic foci. The signalling from the ectopic focus, often located near the pulmonary veins, is fast and irregular (17). The pace is slowed down in the atrioventricular node, but still causes irregular heart rhythm and often tachycardia (18)(see figure 2).
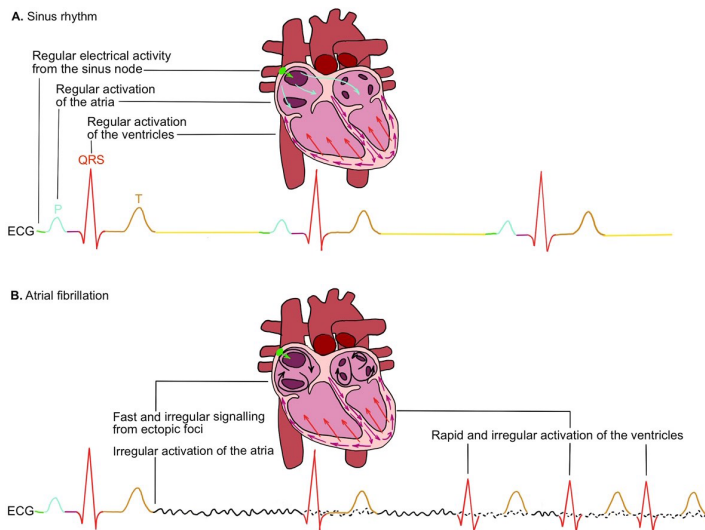

Figure 2. An over-view of electrical signalling during A) Sinus rhythm and B) Atrial fibrillation

Initially during tachycardia an excess of calcium is transported into the myocytes. This in turn causes an increased calcium release from the sarcoplasmic reticulum in the myocyte, leading to even higher levels of calcium in the myocytes (19, 20). The calcium imbalance is believed to cause electrical remodelling that contributes to maintaining the arrhythmia through rate dependant shortening of wavelength by reduced atrial repolarization period and reduced refractory phase (21-24). Parts of the electrical remodelling are reversible but can persist for a few days after conversion to sinus rhythm, which in turn facilitates recurrence of AF (22, 25).

The calcium overload combined with metabolic stress leads to increase in myocyte size and myolysis (26). The myocyte changes could possibly cause inflammation resulting in a common pathophysiological pathway: atrial fibrosis (27). There are many other mechanisms also causing atrial fibrosis, for example hypertension, heart failure or high age. Atrial fibrosis isolates myocytes, creating a milieu where re-entry arrhythmia, like AF, can exist (26, 28, 29).

After some time of tachycardia the calcium deposits in the sarcoplasmic reticulum are reduced, leading to decreased contractility in the atria which eventually may also lead to atrial dilatation (30). Atrial enlargement due to loss of contractility is associated with recurrence of AF (29).

The contractility of the left atrium decreases during episodes of AF. This change could lead to stasis and thrombus formation in the left atrial appendage (see figure 3).
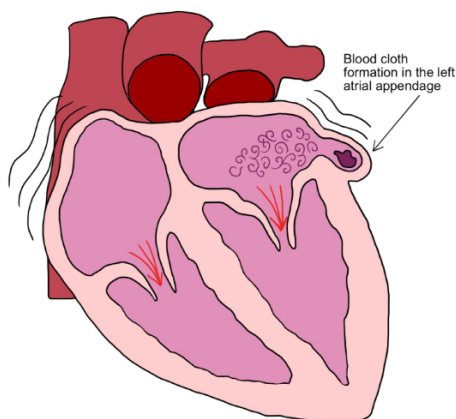

Blood cloth formation in the left atrial appendage

Figure 3. Thrombus formation in the left atrial appendage.

Ischaemic stroke is commonly caused by thrombus embolization from the left atrium to cerebral arteries. However, in patients with high CHA_2DS_2VASc scores (used for stroke risk stratification) and stable vascular atherosclerosis, OAC treatment has been shown to lead to significant reduction of ischaemic stroke risk even in sinus rhythm (31), making other mechanisms contributing to thrombus formation likely. Markers of atrial dysfunction have been shown to be associated with an increased risk of cryptogenic or embolic stroke, but not cerebral small vessel occlusions. The increased risk of only cryptogenic or embolic stroke indicates an atrial origin of the thrombus rather than it being caused by general vascular disease (32). One example of underlying mechanisms is extensive atrial fibrosis (33), which could possibly both pre-dispose for AF and contribute to increased stroke risk even in the absence of AF, by atrial prothrombotic changes. This suggests that all atrial arrhythmia, potentially even micro-AF, may be a sign of atrial cardiomyopathy and could thereby be independently associated with an increased stroke risk.

1.6   Risks related to atrial fibrillation

Stroke is the third leading cause of death in Sweden (34). At least 20% of all strokes are directly attributable to AF (35). In total, AF is diagnosed in 31-38% of patients with stroke (35, 36). The attributable risk of AF for

stroke increases with age, in contrast to other risk factors for stroke (15) and is diagnosed in at least 50% of stroke patients aged ≥80 years (36). Ischaemic strokes related to AF are more severe compared to other ischaemic strokes and also carry increased stroke morbidity and mortality (37, 38).

Oral anticoagulant treatment (OAC) in AF patients is associated with at least a 64% decrease in stroke risk (39). CHA_2DS_2-VASc score is used for stroke risk stratification and treatment guidance (13)(see figure 4).
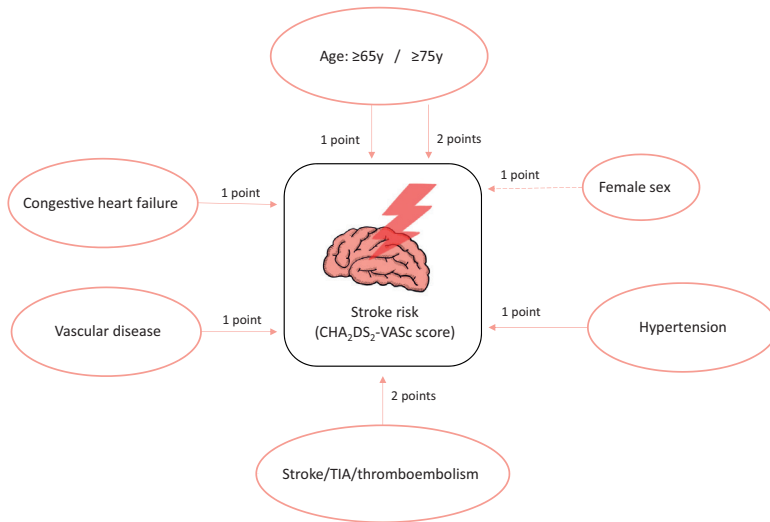

Figure 4. The CHA_2DS_2-VASc score used for assessing the stroke risk in AF patients. TIA indicates transient ischemic attack. Vascular disease includes for example peripheral artery disease and myocardial infarction.

According to current ESC guidelines, OAC treatment is recommended in all women with CHA_2DS_2-VASc score ≥3 and all men with ≥ 2. The benefit of OAC therapy should be weighed against the risk of bleeding; however, many risk factors for haemorrhagic stroke are also risk factors for ischaemic stroke, and most AF patients benefit from OAC treatment (13).

Not only is AF related to ischaemic stroke, it is also associated with several other co-morbidities and increased mortality. AF is associated with an increased risk of dementia, independent of clinically diagnosed stroke (40). A recent register-based study also suggests that OAC treatment is associated with a decreased risk of dementia in AF patients (41).

Individuals with AF have a 22% 10-year incidence of new onset heart failure. The risk factors for AF and heart failure are similar (42). AF is also associated with doubled mortality in both men and women after adjusting for potential confounders (43).

1.7 Population screening for Atrial fibrillation

As AF can be asymptomatic and still associated with an increased risk of stroke, it is important to diagnose AF early to prevent this risk (44, 45). AF screening can potentially facilitate early detection of AF.

Screening can be opportunistic or systematic. Opportunistic screening refers to screening of individuals who receive health care for other reasons. Systematic screening refers to screening of a population invited especially for that purpose, for instance mammography screening for breast cancer in women above a certain age.

In the SAFE study, a multicentre randomised controlled trial among individuals aged ≥ 65-year old, detection rates in primary care centres using either opportunistic or systematic AF screening were compared with detection rates in a control group. In this study, participants in the systematic screening group were invited to attend a screening clinic to have a 12 lead ECG taken. In the opportunistic screening group, an ECG was taken if irregularity was found by pulse palpation during a routine primary care visit. The AF incidences per year were: 1.04% in the control group, 1.64% in the opportunistic screening group and 1.62% in the systemic screening group. The opportunistic screening programme was shown to be the least expensive and easiest alternative, carrying a 60% probability of being cost-effective (46).

In a meta-analysis it was shown that population screening using a single time point ECG in individuals ≥65 years old yielded an overall AF prevalence of 4.4% and a prevalence of new and previously undiagnosed AF of 1.4% (47).

Based on the studies mentioned above the current ESC guidelines recommend opportunistic screening in populations aged >65 years, either by pulse palpation or ECG rhythm strip (13). Using this screening method, individuals with more permanent forms of AF can be identified.

By systematic screening using a handheld one-lead device performing intermittent 30-second ECGs twice daily for two weeks in the STROKESTOP I study, the AF prevalence in an unselected population of 75- and 76-year-olds increased by 3 percentage points, from 9.3% to 12.3%. Only a small proportion of the screened population had AF detected on index-ECG, 0.5% (9). In a study with similar design and population, but with at least one more stroke risk factor apart from age, the known AF prevalence increased by 7.4 percentage points after screening (48). There is variance in the AF prevalence between primary preventive systematic screening studies, depending on population included and screening methods used (see figure 5).
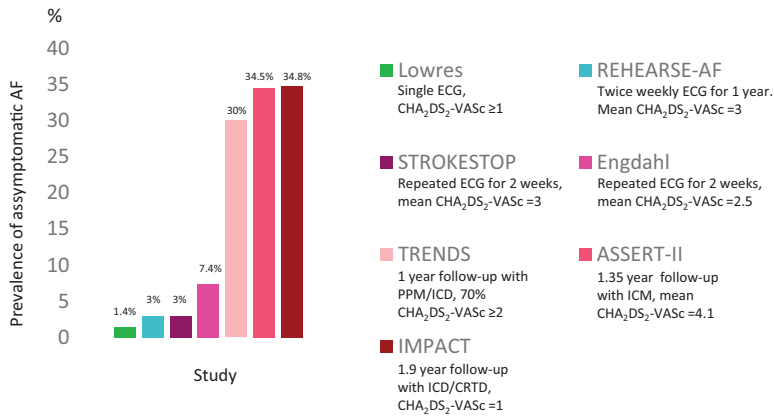
Figure 5. Prevalence of asymptomatic atrial fibrillation by screening method and stroke risk score. Reprinted courtesy of European Heart Journal: 2020;41(10) Oxford University Press © Colors and font re-made for use in this thesis. CRT-D indicates Cardiac resynchronization therapy with defibrillator. ICD indicates implantable cardioverter defibrillator. PPM indicates permanent pacemaker.

According to ESC guidelines systematic screening may be considered in individuals >75-years old or with high risk of stroke (13).

1.8 Atrial fibrillation screening in stroke patients

In patients with prior stroke or TIA and without known AF extended ECG monitoring in addition to standard follow-up after such events (often 24 hours ECG monitoring) have been shown to significantly increase the AF detection. In one study the prevalence previously unknown AF increased from 2.6% after 24 hours ECG monitoring to 4.3% after 72 hours ECG monitoring (49). In another study, seven days of continuous event-recording detected AF in 5.7% of participants without AF found on neither 12 lead ECG or 24 hour Holter ECG. (50). In a study using long-term monitoring with an insertable cardiac monitor for 12 months, the AF prevalence increased by 10.4 percentage points (10).

In patients >65-years old suffering from TIA or ischaemic stroke and not diagnosed with AF, a 30-second intermittent recording twice daily for 30 days was compared to five days continuous ECG. Intermittent recording detected AF in 21% of participants compared to 18% by continuous ECG. Only 11% were diagnosed using both methods (51).

Previous TIA or stroke has in addition to age been shown to be the most important risk factors for new stroke in AF patients (52). Accordingly ESC guidelines recommend screening for AF by an ECG rhythm strip followed by at least 72 hours ECG monitoring in patients with TIA or ischaemic stroke. Long-term non-invasive loop-recorders or implantable loop-recorders may also be used in patients with ischaemic stroke (13).

1.9   Different screening devices

There are many different screening methods for AF detection. Commonly used screening methods are summarised in a report from the AF-SCREEN International Collaboration (53). Pulse palpation, oscillometric blood pressure monitors with AF detection function and photoplethysmography, can all identify individuals with irregular pulse, but an ECG is recommended for AF diagnosis. There are many different handheld devices used for single time-point screening or prolonged intermittent screening. The hand-held devices are user-friendly and have a higher sensitivity and specificity for AF detection than pulse-based screening methods (54). Long periods of internal and external continuous monitoring might detect paroxysmal AF more effectively than repeated intermittent screening with a hand-held device. Using continuous external ECG recording introduces potential problems with compliance, often due to skin irritation from electrodes and patches (55). Wristwatches with ECG recording capacity have now also become available for AF-screening (56).

The two devices used in this thesis have both been validated previously. The hand-held intermittent ECG from Zenicor has been validated for AF detection compared to 12-lead ECG and has a 96% sensitivity and a 92% specificity (57). Intermittent ECG recordings have been further studied in a cohort of patients with known paroxysmal AF. AF episodes were detected in 82% using intermittent recordings 10 seconds twice daily during a 30-days period compared to 32% detected by the 24-hour continuous recording (58). In a validation study, the algorithm of the continuous event-recorder, R-test 4 from Novacor, had a 92% sensitivity and 87% specificity for AF detection in comparison to continuous ECG (59).

1.10   Stroke risk, AF classification and AF symptoms

Common symptoms related to AF are dyspnoea, chest discomfort, palpitations, fatigue, dizziness and syncope (60). About one third of AF patients are thought to be asymptomatic (61). An association between asymptomatic AF and higher age, as well as more co-morbidities and permanent AF has been seen. Regardless of symptoms patients with AF have an increased risk of stroke and seem to have an increased risk of death (44, 45). A recent systematic review found no difference in stroke risk depending on presence of symptoms and concluded that symptomatic status should not be taken into account in determination of treatment approach (62).

Participants in a cohort study with incidentally diagnosed AF were found to have a two-fold increase in incidence of stroke compared to individuals with no AF. OAC treatment reduced stroke risk by >60% and mortality by >40% in this group. Half the individuals with incidentally diagnosed AF were already initiated on OAC treatment, making it likely that the stroke risk was underestimated (63). One might hypothesise that the risks identified in this study may serve as an indicator of the risks associated with screening-detected AF.

There is contrasting evidence also with regards to the risk of stroke depending on type of AF. Stroke rates in individuals with permanent AF have in several studies been shown to be equal to paroxysmal AF after adjustment for stroke risk factors (39, 64, 65). In contrast, other studies have shown that persistent and permanent forms of AF are associated with an increased risk of stroke compared to paroxysmal AF, even after adjusting for CHA$_2$DS$_2$-VASc score (66-68).

The ESC guidelines do not endorse taking AF type, AF burden or symptoms into account in stroke risk assessment. Evaluation of stroke risk in AF patients should only be based on CHA$_2$DS$_2$-VASc score. ECG verified screening-detected AF is treated the same as clinically diagnosed AF (13).
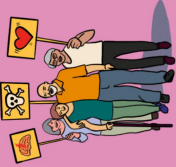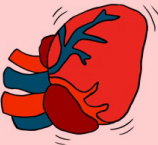
1.11 Prevalence of supraventricular ectopy

A supraventricular ectopic beat (SVEB) is a premature complex arising from the atria or the atrioventricular junction, instead of from the sinus node, which normally initiates cardiac activation. SVEBs can be unifocal or multifocal. They can appear randomly or with regular intervals, resulting in bigeminal or trigeminal rhythm. Increased automaticity is the most common underlying mechanism of SVEBs (69). Episodes of ≥3 consecutive SVEBs with a rate >100 beats per minute are called supraventricular tachycardias (SVTs).

One study using 24-hour Holter monitoring evaluated the SVEB burden in individuals with normal cardiac catheterization in the United States Air Force Aeromedical Consultation Service. No SVEBs were found in 11.9%, ≤ 0.1% SVEBs were found in 72.9% and >0.1% SVEBs were found in 5.2% of participants. SVTs with a duration of 3-10 beats was found in 4.3% of participants (70). Another study focused on individuals aged ≥75 years without acute medical conditions. It found that 21% of these individuals had SVEBs seen during 24-hour ECG monitoring and 1% had SVTs (71). In a study among healthy 60-85 year olds, SVEBs were found in 88% and SVTs were found in 13% of the participants 24-hour ECGs (72). Inspection of recordings from patients in all ages who underwent examination after syncope at The Medical Centre Hospital of Vermont displayed presence of SVEBs during 24-hour ECG monitoring ranging from 15% below age 30 years to 58% in patients ≥70 years. SVTs were found in 1% of participants <30 years old and in up to 40% in participants aged ≥ 70 years (73).

1.12 Relationship between supraventricular ectopy, AF and stroke

Several studies have shown that supraventricular ectopy - both isolated SVEBs and SVTs - during 24 hours ECG monitoring is associated with an increased risk of AF and stroke (74-76). Similar results were seen when SVEBs were detected during single time-point ECG (77, 78). Important studies of SVEBs and SVTs are listed (see table 1) and some of these studies are discussed in more detail below.

Study	Population	Method	AF detection	Stroke risk
Engstrom et al. Stroke, 2000 (76)	AF free participants, without previous stroke or myocardial infarction, n=402, mean age 68 years and 100% men.	High frequency of SVEBs was defined as ≥218 on 24-hour ECG (the top fifth quintile). End-point retrieval through registry follow-up, 11.1 years (mean).	–	Participants with high frequency of SVEBs had a relative risk of 1.9 (95% CI, 1.0-3.4, p=0.04) Stroke was diagnosed in 15/77 (19.5%).
Binici et al. Circulation, 2010 (79)	AF free participants, without earlier history of cardiovascular disease or stroke, n=678, mean age 64.5 years and 59% men.	Excessive supraventricular activity termed ESVEA (>30 SVEBs/h or any SVT >20 consecutive beats) was identified on 48-hour ECG. End-point retrieval through registry follow-up, 6.3 years (mean).	In participants with ESVEA the hazard ratio was 2.8 (95% CI 1.1-7.0, p=0.033). AF was diagnosed in 7/99 (7%) with ESVEA.	In participants with ESVEA the hazard ratio was 2.8 (95% CI 1.2-6.3, p=0.014) Stroke was diagnosed in 10/99 (10%) with ESVEA.
Chong et al. Europace, 2012 (80)	AF free participants with palpitations, dizziness or syncope, n=428, mean age 66.7 and 44% men.	High frequency of SVEBs were defined as ≥100 per 24-hour ECG (top fourth quartile). End-point retrieval through registry follow-up, 6.1 years (mean).	In participants with frequent SVEBs the hazard ratio was 3.22 (95% CI 1.9–5.5; p< 0.001). AF was diagnosed in 31/107 (29%) of those.	In participants with frequent SVEBs the hazard ratio was 2.1 (95% CI 1.1-4.8, p<0.001). Stroke was diagnosed in 16/107 (15%) of those.

Study	Population	Methods	Results	
Dewland et al. Ann Intern Med, 2013 (75)	A random subset of AF free participants, n=1260, mean age 71 years and 45% men.	Individuals with 9.5–965.4 SVEBs/hour (top fourth quartile) were identified on 24-hour ECG. End-point retrieval through registry follow-up, 13 years (mean)/annual study ECGs/repeat Holter-ECG after 5 years.	In participants with frequent SVEBs the hazard ratio was 4.9 (95% CI 3.4–7.2, p<0.001). Median SVEB count for participants diagnosed with AF was 5.3 (IQR 2.1–18.0).	–
Inohara et al. PLoS One, 2013 (77)	Participants without history of myocardial infarction, stroke or AF were included, n=7692, mean age 52.5 years and 41% men.	Individuals with presence of SVEBs were identified on 12-lead ECG. End-point retrieval through registry follow-up, 14 years (mean).		Death due to stroke was seen in 5/64 (7.8%) with SVEBs compared to 133/7628 (1.7%) without SVEBs, p<0.001.
Kochhauser et al. Stroke, 2014 (81)	AF free participants with acute cryptogenic stroke, n=70, mean age 58.8 years, CHA₂DS₂-VASc score 3.8 and 61% men.	Individuals with >14.1 SVEBs/h and >0.2 SVTs/h (top fourth quartile) were identified on 24-hour ECG. An internal loop recorder was implanted in all participants, with a mean monitoring time of 1.5 years.	In participants with frequent SVEBs the relative risk was 4.0 (95% CI 1.1–14.6, p=0.04) and in participants with frequent SVTs the relative risk was 6.9 (95% CI 1.8–26.7, p=0.005).	–
Johnson et al. Heart Rhythm, 2015 (74)	AF-free participants, n=383, with mean age 64.6 years and 45% were men.	ESVEA was identified on 24-hour ECG. End-point retrieval through registry follow-up 10.3 years (mean).	In participants with ESVEA the hazard ratio was 3.0 (95% CI 1.6-5.8, p<0.001).	–

Study	Participants	Methods	Outcome (AF)	Outcome (stroke/death)
Murakoshi et al. Eur Heart J, 2015 (78)	Participants without self-reported heart disease at baseline, n=63,197, with mean age 58.8 years and 32% were men.	Individuals with presence of SVEBs were identified on 12-lead ECG. End-point retrieval through registry follow-up, 14.3 years (mean).	In women with SVEBs the hazard ratio was 3.8 (95% CI 2.7-5.6, p<0.001). In men with SVEBs the hazard ratio was 4.8 (95% CI 3.6-6.6, p<0.001).	In women with SVEBs the hazard ratio of stroke death was 1.6 (95% CI 1.3-2.0, p<0.001). In men with SVEBs the hazard ratio of stroke death was 1.2 (95% CI 1.0-1.6, p<0.001).
Larsen et al. J Am Coll Cardiol, 2015 (82)	AF free participants, without earlier history of cardiovascular disease or stroke, n=678, mean age 64.5 years and 59% men.	ESVEA was identified on 48-hour ECG. End-point retrieval through registry follow-up after 15 years.	AF was diagnosed in 18/99 (18%) with ESVEA.	Excluding patients diagnosed with AF before their stroke, for individuals with ESVEA the hazard ratio was 1.96 (95% CI 1.1–3.5, p = 0.02) Stroke was diagnosed in 21/99 (21%) with ESVEA.
Marinheiro et al. Int J Cardiol, 2017 (83)	Participants without previous diagnosis of AF or stroke were included, n=362, mean age 71 years and 56% were men.	Individuals with frequent SVEBs, >97 per hour (top fifth percentile) were identified on 24-hour ECG. End-point retrieval through registry follow-up after 7.1 years.	In participants with frequent SVEBs the hazard ratio was 2.1 (95% CI 1.3-3.2, p=0.01). >30 SVEBs/h was also independently associated with a higher risk of AF.	In participants with frequent SVEBs the hazard ratio was 2.8 (95% CI 1.7-4.8, p<0.001).
Johnson et al. Heart Rhythm, 2018 (84)	AF-free participants, n=377, with mean age 64.5 years and 43% were men.	SVT episodes ≥5 beats were identified on 24-hour ECG; participants were classified based on SVT characteristics. End-point retrieval through registry follow-up, 13.2 years (mean).	The highest hazard ratio was 4.95 (95% CI 2.1–11.9, p <0.001) in participants with irregular SVTs lacking p-waves. AF was diagnosed in 9/19 (47.4%) in that group.	The highest hazard ratio was 14.2 (95% CI 3.8–57.6, p<0.001) in participants with regular SVTs lacking p-waves. Stroke was diagnosed in 7/24 (29.2%) in that group.

In a study by Binici et al. healthy men and women aged 55-75 years old were examined with 48-hour Holter recordings and followed up in registers. A three-fold risk of clinically diagnosed AF and a >60% increase in risk of stroke and death was seen in individuals with ≥ 20 SVEBs in runs or ≥ 30 SVEBs/hour after a mean follow up of 6.3 years. The >30 SVEBs/hour division represent the top tenth percentile SVEB frequency in the population studied (79). Larsen et al. concluded from the same study material that participants with these findings and CHA_2DS_2-VASc -score ≥ 2 have a stroke incidence comparable to individuals with AF at 2.4 % per year. The stroke risk was increased even after exclusion of individuals diagnosed with AF prior to stroke from the analysis (82). Frequency of SVEBs, as well as length of a SVEB runs were linearly associated with incidence of AF. Participants with SVEB runs of 5-10 beats had an annual risk for AF of approximately 0.7 %, the risk was increased five-fold compared to the risk in those without SVEB runs (79).

In a similar study by Marinheiro et al., individuals with a mean age slightly above 70 years had undergone 24-hour ECG monitoring. The ECGs were assessed for frequency of SVEBs. Only in the group with the top fifth percentile SVEB frequency, >97 per hour, frequent SVEBs were independently associated with an increased stroke risk of 3,5% per year (83).

In another study by Johnson et al., individuals with a mean age of 65 years who had undergone 24-hour Holter ECG were followed in registers for a mean of 10.3 years. Their 24-hour Holter ECGs were scrutinized for number of SVEBs per hour, number of SVTs per hour, maximum heart rate during SVT, duration of SVTs and excessive supraventricular activity, meaning ≥30 per hour or ≥20 SVEBs in a run. Both number of SVEBs/hour, SVTs/hour and excessive supraventricular activity did independently predict future AF. The SVT duration and heart rate did not predict future AF (74).

In patients with AF symptoms, high burden of SVEBs was in study by Chong et al. associated with a three-fold increase in risk of stroke compared to a low burden of SVEBs, with the difference remaining significant even after adjusting for potential confounders (80).

In a study of stroke patients by Kochhauser et al., a high burden of SVEBs was associated with a four-fold increase in risk of future AF and high a burden of SVTs was associated with a seven-fold increase in risk of future AF (81).

Johnson et al. found that there was a stronger association between short irregular SVTs without p-waves and AF, compared short regular SVTs without p-waves, that seemed less likely to progress into AF (84).

Although all these studies suggest an increased risk of AF and/or stroke the endpoints have all been from registries. In particular for asymptomatic AF there might be risk of underdiagnosis. In addition, there are no published studies assessing the value of OAC treatment in patients with excessive supraventricular activity.

1.13   Stroke risk in patients with device detected atrial high rate episodes

In patients with an implanted pacemaker or defibrillator equipped with an atrial lead, the device can automatically detect and record atrial tachyarrhythmia. The data recorded have been used in several studies to evaluate if these atrial high rate episodes (AHRE) are associated with AF and stroke. The definition of AHRE varies in different studies, but a common definition is an episode >5-6 minutes with a rate of >180 beats per minute (13, 85).

AHRE are common in pacemaker patients, 10-35% depending on the group studied (86, 87). In a meta-analysis AHRE strongly predicts clinical AF with an odds ratio of 5.7 and is associated with a 2.4-fold increase in stroke risk. The exact cut-off for AHREs differs between studies (87). Stroke risk scores, important in comparing the stroke risk in patients with AHRE to the stroke risk in clinically diagnosed AF, are not available for all studies. It is known that the stroke risk in patients with AHRE is lower than in patients with clinically diagnosed AF. AHRE can also be heart rhythms other than AF (87, 88). Stroke in patients with AHRE often appear without temporal relation to the high rate episodes (89-93), indicating that AHRE may be a risk marker rather than a direct cause for thromboembolism in these patients. However, AHRE lasting >24 hours display a strong association with stroke (94). Interestingly, there is no correlation between AHRE and history of stroke, suggesting that AHRE might be caused by implantation of pacemaker lead (86, 95). AHRE is common, however, not only in patients with pacemakers and defibrillators, but also in individuals with subcutaneous implantable devices, CHA_2DS_2-VASc score ≥2-3 and additional risk factors for AF (96, 97).

According to ESC guidelines, further ECG monitoring is regarded in patients with AHRE, to verify the AF diagnosis. OAC treatment is recommended only when the AF diagnosis can be verified by ECG (13). Large prospective randomised studies assessing the effect of OAC in patients with AHRE are under way (98, 99).

2 AIMS OF THE THESIS

2.1 Overall aim

The hypothesis was that extended screening and follow-up in elderly patients with a high risk of stroke (CHA$_2$DS$_2$-VASc-score $\geq$ 2) and short episodes of atrial-fibrillation (AF)-like activity (micro-AF) detects a significant proportion of silent and previously undiagnosed AF compared to patients without micro-AF. The following intermediate aims were set up:

2.2 Specific aims of the thesis

- To study the prevalence of micro-AF in an elderly population

- To postulate the time span from micro-AF to clinically manifest AF

- To assess if number and duration of micro-AF episodes predict development of AF

- To compare AF detection between continuous and intermittent ECG recording

- To compare participants' willingness to use continuous and intermittent ECG

- To study the prognosis, including mortality, stroke and development of AF in patients with micro-AF, other supraventricular tachycardias and frequent supraventricular ectopic beats (isolated, bigeminal or trigeminal)

3   MATERIALS AND METHODS

3.1   Study population

The participants in study I and IV derived from STROKESTOP I, a population-based cohort study, to which all 75- and 76-year olds living in the Stockholm County or Halland region were randomised 1:1 to be included in the AF screening programme. Inclusion was ongoing from 2012 to 2014. All participants in the screening group without previously known AF (n=6955) were asked to perform 30 seconds ECG recordings twice daily for two weeks using an intermittent device from Zenicor. Upon inclusion the participants were asked to fill out questionnaires with regards to medical history and to self-assess their weight and height (only Stockholm arm). They also had their pulse controlled and blood pressure measured (9).

The participants in study II and III were recruited from the STROKESTOP II study population. STROKESTOP II was also a mass-screening study for AF in 75- and 76-year olds. All residents in Stockholm County were randomised 1:1 to participate in the screening procedure or to serve as a control group. Participants were included from 2016 to 2018. Only individuals in the screening group without known AF and with N-terminal pro b-type natriuretic peptides (NT-proBNP) levels ≥125 ng/L (n=3766) participated in the two-week, extended AF screening using intermittent ECG four times daily (100). The study protocol of STROKESTOP II is similar to the earlier protocol of STROKESTOP I in most aspects. The main differences were that participants were instructed to make more frequent intermittent recordings and the group performing extended screening using intermittent ECG during STROKESTOP II was smaller as NT-proBNP was used to identify high-risk individuals to reduce the screening burden.

3.2   Screening methods

Two different ECG devices were used for AF screening in the studies included in this thesis; hand-held intermittent ECG using a Zenicor II device (Zenicor Medical Systems, Stockholm, Sweden, see figure 6) and continuous event-recording using an R-test 4 evolution device (Novacor, Rueil Malmasion, France, see figure 7). Both of these one-lead devices are already used in clinical practice and have been previously evaluated with regards to AF detection.

The intermittent ECG has a 92% sensitivity and a 96% specificity for AF detection compared to 12-lead ECG (57). Every registration has a duration of 30 seconds, and placing thumbs at two electrodes performs the recording. The data is transmitted to the software immediately. The device has a button for marking if symptomatic arrhythmia occurs.

Figure 6. Handheld intermittent ECG device - Image courtesy of Zenicor

The algorithm of the continuous event-recorder has a 92% sensitivity and a 87% specificity for AF detection compared to continuous ECG (59). It has a monitoring capacity of 32 days and can store up to 60 minutes ECG. The device can be set to store a certain number of episodes of each arrhythmia of interest. It can also be activated manually if symptomatic arrhythmia occurs.

Figure 7. Continuous event-recorder - Image courtesy of Novacor

The participants in all our studies were asked to fill out a form to report if and when they had symptoms during screening.

3.3   Diagnostic criteria for micro-AF and AF

Micro-AF was defined in study I as abrupt onset episodes of ≥4 consecutive supraventricular beats with irregular rate-to-rate intervals and absence of regular p-waves, lasting for <30 seconds. As an effort to make micro-AF easier to identify in clinical practise, we decided to change the criteria before inclusion started in the later studies. In studies II and IV, micro-AF was defined as abrupt onset episodes of tachycardia (>100 beats/minute) with ≥5 consecutive supraventricular beats, irregular rate-to-rate intervals, absence of regular p-waves and lasting for <30 seconds (see figure 8). AF was defined according to ESC guidelines as an irregular heart rhythm with absence of p-waves, lasting for at least 30 seconds (13).
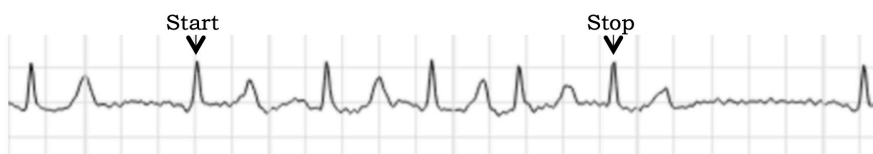

Figure 8 – Example of a micro-AF episode.

3.4   Study I

Towards the end of inclusion in STROKESTOP I the investigators noticed that some participants had shorter runs of AF-like activity and began to mark them for follow-up. After 2.3 years participants with micro-AF still free from AF along with a control group matched for CHA_2DS_2-VASc score and inclusion date were invited to participate in this prospective cohort study. Participation rate was 64% (n=47/74) in the micro-AF group, and the control group included an equal number of participants (see figure 9). The participants were once again asked to fill out a questionnaire regarding their medical history and had their pulse and blood pressure measured. The participants did repeat AF screening, performing intermittent ECG for 30 seconds, twice daily along with continuous event-recording in parallel for two weeks. Participants who had significant arrhythmia detected were offered cardiologist follow-up.
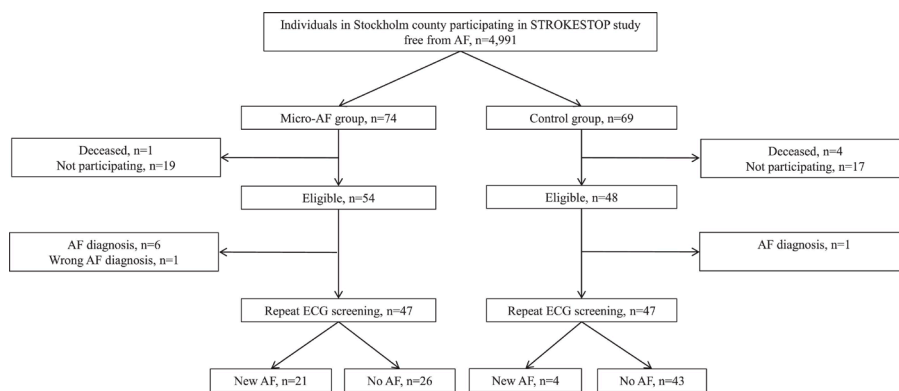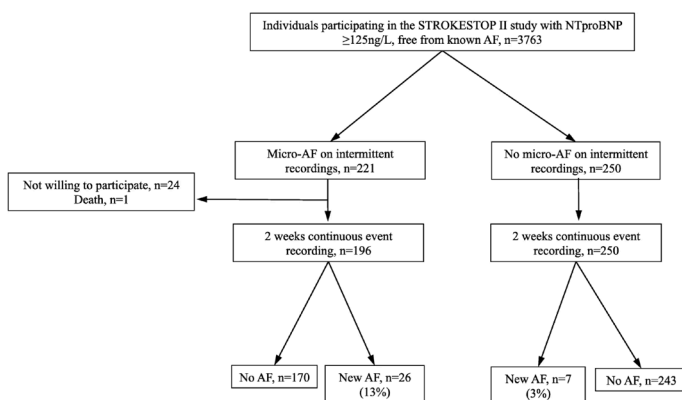
Figure 9. *Participation and screening procedure in study I. Reprinted courtesy of The American Journal of Cardiology: 2018;122(7) Elsevier Inc.©*

3.5 Study II

Study II was also a prospective cohort study. During STROKESTOP II an algorithm was used to detect ECGs with arrhythmia (101). Specially trained nurses manually annotated all suspected micro-AF episodes. The investigators verified each micro-AF episode. Individuals with micro-AF were asked to participate in extended AF screening using continuous event-recording for two weeks. An unmatched control group in STROKESTOP II did continuous event-recording in parallel with intermittent ECG. Individuals in the control group with micro-AF seen during intermittent ECG were transferred to the micro-AF group, resulting in a micro-AF group with 200 participants and a control group with 250 participants (see figure 10).

Figure 10. *Participation and screening procedure in study II. Reprinted courtesy of BMC Cardiovascular disorders: 2020;10;20(1):167 The authors ©*

3.6   Study III

Study III was a prospective method comparison study. It included the participants who did recordings using two screening methods in parallel during STROKESTOP II, most of whom were also included in the control group in study II. During their two weeks ECG registration, they were also asked to fill out a questionnaire with regards to comparing compliance and ease of use of the two devices. The following questions were included:

1) Was the device difficult to use?	2) Which problems did you have with the device?	3) Were you able to finish the recording?
4) If not, what was the problem leading to discontinuation?	5) Did the recording affect your daily life?	6) Did the recording have effect on your experienced health?

Question 1 was answered on a graded ordinal scale from 1-5. Question 2 and 4 were answered in free text. Questions 3, 5 and 6 were answered as yes/no. The answers to questions 2 and 4 were analysed together, as the questions were found to be asking for the same information. The answers to question 3 were found to be abundant as we had direct access to actual registration times for each individual and could therefore compare those.

3.7   Study IV

In this retrospective cohort study, all ECGs belonging to AF-free individuals in STROKESTOP I were re-evaluated using an automated algorithm to detect all cases of micro-AF. The algorithm also identified SVTs without AF characteristics, episodes of SVEBs in bigeminy/trigemiy and individuals with frequent isolated SVEBs (top tenth percentile). The arrhythmias detected by the algorithm were manually examined to confirm the findings. Participants were divided into arrhythmia group by the most pathological arrhythmia identified (see figure 11). All participants were followed for at least three years in patient registers from the National Board of Health and Welfare and in the Cause of Death Register. The primary endpoint was AF and secondary endpoints were stroke and death. Comorbidity data was also collected from registers.
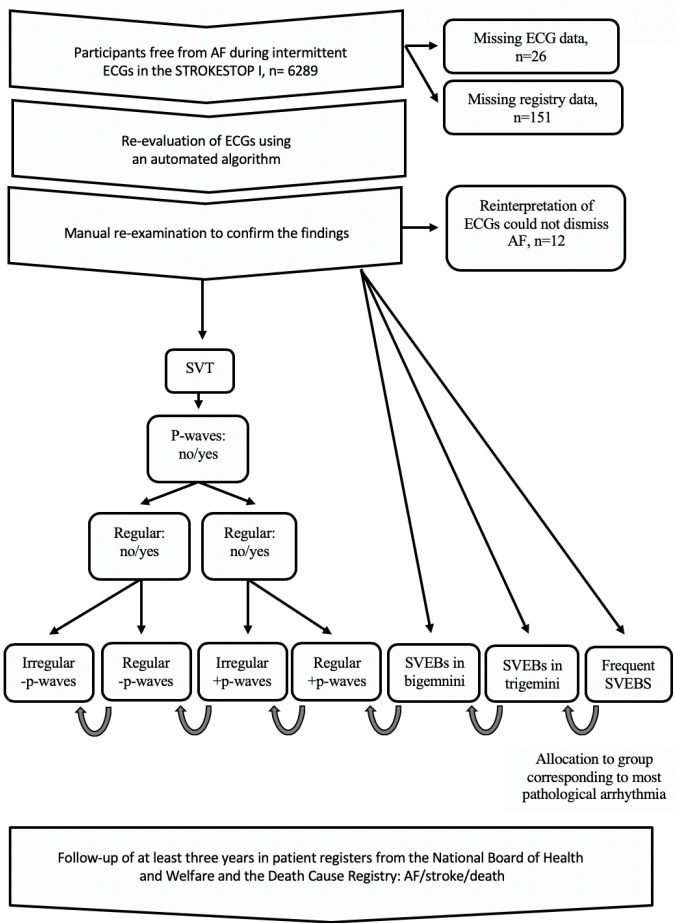
Figure 11. Method study IV.

4   STATISTICS

4.1   General

For all continuous variables included in the studies of this thesis, histograms for assessment of normal distribution were visually interpreted and Shapiro-Wilks test was performed. Non-normally distributed continuous variables are reported as median (IQR) and analysed using Mann-Whitney U- test. Normally distributed variables were reported as mean ±(SD) and analysed using: Paired Sample t-test in study I, Independent Samples t-test in study II, Paired Sample t-test in study III and Independent Sample t-test in study IV. Ordinal variables were reported as median (IQR) and analysed using Mann-Whitney U- test. For dichotomous variables presented as proportions, Chi-square and Fisher's exact test was used. Comparisons of the screening methods were performed using McNemar's test.

No power calculations were performed for the studies included in this thesis; study I was a pilot-study, study II included all participants with micro-AF in the cross-sectional STROKESTOP II, study III was an explorative study and study IV included all participants from the cross-sectional STROKESTOP I study.

For all statistical analyses, the significance threshold for the p-value was set to <0.05. The analyses in study I-III were performed using IBM SPSS statistics, version 24 software (IBM SPSS Statistics, IBM Corp, Somers, NY). For analysis in study IV Stata versions 14 and 16 (Stata Corp., College Station, TX, USA) was also used.

4.2   Study I

The micro-AF group had matched controls and the groups were compared pairwise. For uni-and multivariable analyses, logistic regression analysis was used. All variables that were significant during univariate analysis were included in multivariable analysis.

4.3   Study II

Micro-AF participants were compared to an un-matched control group as independent samples. Logistic regression was used for multivariable analyses. Most significant variables from univariate analysis were included. The number of SVEBs per 30-second intermittent ECG, however, was not included in the multivariable analysis due to interaction with presence of micro-AF. Time between use of the two different ECG methods was also excluded from the multivariable analysis as it correlated to participation in the micro-AF group and implied a risk for reversed causation. In addition, potential confounders as identified by the HATCH-score (hypertension,

stroke/TIA and heart failure) – which is one risk score to predict AF – were included in the multivariable model. A stratified analysis was used to compare micro-AF as a predictor for AF in men and women separately.

4.4   Study III

This is a method-comparison study, the participants were their own controls. No multivariable analysis was performed.

4.5   Study IV

The different arrhythmia groups were unmatched and compared as independent samples. The CHA_2DS_2-VASc score parameters were considered potential confounders and were adjusted for during Cox regression analysis, except from thromboembolism due to risk of co-variation with AF. Kaplan-Meier curves were used to present the clinical AF detection rate per arrhythmia group.

5   ETHICAL CONSIDERATIONS

All research projects included in this thesis, except study IV, depend on participation of patients and healthy controls. All studies comply with the Declaration of Helsinki, the protocols are approved by the regional ethics committee and all participants gave their informed consent. Still, to screen for a disease in individuals free from symptoms can be controversial when the treatment offered entails risks. In this case untreated AF was believed to impose greater risk than the treatment itself.

Some individuals suffered from discomforting itching and eczema from the continuous event-recorder patches. In addition to physical discomfort, participation could also cause anxiety, a psychological discomfort. Participants with micro-AF were told about the irregularity in heart rhythm and received information about the increased risk of AF. Individuals with no AF found during repeat screening may have continued to worry about developing AF or may have regarded themselves as free from AF even though the screening result could be falsely negative and the disease may be of progressive nature.

The potential benefits of participation for the individual participants and the society were considered to be large, as strokes produce high patient suffering and high costs. The potential risks and suffering connected to participation were small.

The privacy violation is considered exiguous as sensitive personal data was collected first after informed consent was given. All personal data was stored in a safe database provided by Zenicor. Participants were also followed in patient registers from the National Board of Health and Welfare as well as in the Cause of Death Registry.

The person who invited a potential participant was not the treating physician, and the potential participant did not depend on him/her in any medical or health care sense. This lowered the risk of patients experiencing the feeling of being forced to participate. Early dropouts from a study also did not affect the follow-up; all participants in whom significant arrhythmia was found were offered a cardiologist follow-up. Individuals that could potentially have suffered from the inconvenience of participating in the study were the same as the group of the Swedish population that could most likely benefit from the impact of a positive result.

All participants diagnosed with AF in the studies were after individual risk examination initiated on OAC treatment in accordance with ESC guidelines (13). The treatment itself is known to increase the risk of bleeding, but in the majority of patients with AF, the risk of ischemic stroke outweighs the bleeding risk.

6   RESULTS PER STUDY

6.1   Study I

Participation in the micro-AF group – including individuals clinically diagnosed with AF during follow-up, was 73% (n=54/74) and 74% (n=48/65) in the control group. Median time to follow-up was 2.3 years. The time to follow-up was longer in the control group (p<0.001), where participants hence got older (p<0.001). Control group participants also had higher systolic blood pressure (p=0.03). The micro-AF group had more SVEBs than the control group (p<0.001). Apart from this, the groups were similar in baseline characteristics.

In the micro-AF group, 45% (21/47) were diagnosed with AF during repeat screening. Including individuals clinically diagnosed with AF during the two-year follow-up period, 50% (27/54) received an AF diagnosis. One individual in the control group had been diagnosed with AF during follow-up. Including this individual and after repeat screening, 10% (5/48) of participants in the control group had received an AF diagnosis. The difference is significant, p<0.001. All participants with AF diagnosed before and during screening were initiated on OAC treatment. For patients in the micro-AF group more SVEBs, more frequent episodes of micro-AF and longer episodes were associated with the development of AF. In multivariable analysis only increased amount of SVEBs remained significant (see table 2).

Variable	Unadjusted OR (CI 95%)	p value	Adjusted OR[†](CI 95%)	p value
Time interval between ECG examinations (days), n median (IQR)*	0.994 (0.989–0.999)	0.013	0.997 (0.991–1.003)	0.227
Number of SVEBs per 30 seconds ECG in STROKESTOP study, n median (IQR)	1.682 (1.216–2.328)	0.002	1.446 (1.016–2.060)	0.041
Number of micro-AF episodes, n median (IQR)	1.536 (1.091–2.163)	0.014	0.962 (0.681–1.361)	0.829
Longest micro-AF episode (n of complexes) median (IQR)	1.302 (1.132–1.499)	<0.001	1.181 (0.993–1.404)	0.060

AF = atrial fibrillation; IQR = interquartile range; OR = odds ratio; SVEBs = supraventricular ectopic beats.

* per day.

† Adjusted for amount of supraventricular ectopic beats, number of micro-AF episodes, length of longest micro-AF episodes and duration between inclusion dates in the 2 studies.

Table 2. Multivariable analysis for the development of AF. Reprinted courtesy of The American Journal of Cardiology: 2018;122(7) Elsevier Inc.©

More cases of AF were detected using continuous event-recording (n=25) than intermittent ECG (n=10), p<0.001. No AF cases were detected only by intermittent ECG.

6.2 Study II

Of participants in STROKESTOP II, 6% had micro-AF. Of that micro-AF cohort, 89% (n=196/221) participated in the micro-AF follow-up study. Participants in the control group were older (p<0.001), more frequently had diabetes mellitus (p<0.001), were shorter (p=0.035), had less SVEBs (p<0.001) and had higher CHA_2DS_2-VASc scores (p=0.01). The CHA_2DS_2-VASc scores were similar to study I. As per study design participants in the micro-AF group had longer follow-up time to extended screening (3.3 months) compared to the control group who were screened using both ECG modalities in parallel, p<0.01. In both study I and II, participants with micro-AF had significantly longer analysable signalling time for the continuous event-recorder. Most participants in study I and II had only one episode of micro-AF, and the episodes were short (5-6 beats on average).

As in study I total AF prevalence was four-five-times higher in the micro-AF group compared to the control group. In the micro-AF group, AF was detected in 13% (n=26/196) of participants and in 3% (n=5/33) in the control group. All individuals with detected AF were also in this study initiated on OAC treatment.

Participants diagnosed with AF were taller, had longer analysable signalling time for continuous event-recording, more frequent micro-AF episodes with longer duration and more SVEBs (p<0.001 for all comparisons). Presence of micro-AF remained a strong predictor for AF through the different multivariable models (see table 3), but micro-AF burden (duration and frequence of episodes) did not.

Variable	Unadjusted OR (CI 95%)	P	Model 1 Adjusted OR (CI 95%)	P	Model 2 Adjusted OR (CI 95%)	P	Model 3 Adjusted OR (CI 95%)	P
Micro-AF	5.3 (2.3–12.5)	< 0.001	4.7 (2.0–11.1)	< 0.001	5.1 (2.1–12.8)	< 0.001	4.6 (1.8–11.5)	< 0.001

Model 1: Adjusted for height and analysed signal time
Model 2: Adjusted for age, hypertension, heart failure and stroke
Model 3: Adjusted for height, analysed signal time, age, hypertension, heart failure and stroke
AF atrial fibrillation, *CI* confidence interval, *Micro-AF* short episodes of irregular supraventricular tachycardia, always refers to when it is seen during intermittent ECG recordings; *OR* odds ratio, *SVEBs* supraventricular ectopic beats

Table 3. Multivariable analysis for the development of AF. Reprinted courtesy of BMC Cardiovascular disorders: 2020;10;20(1):167 The authors ©

Further multivariable analysis showed that micro-AF was a stronger predictor for AF in men than in women.

6.3   Study III

Seven percent (n=269) of the participants in STROKESTOP II were included in this sub-study from June 2017 to January 2018. AF was detected in 6% (n=15) of those participants when using continuous event-recorder and in 2% (n=5) when using intermittent ECG. All cases of AF detected by intermittent ECG were also detected by continuous event-recording. Continuous event-recording had detected significantly more AF compared to intermittent ECGs already after three days of screening (see figure 12).
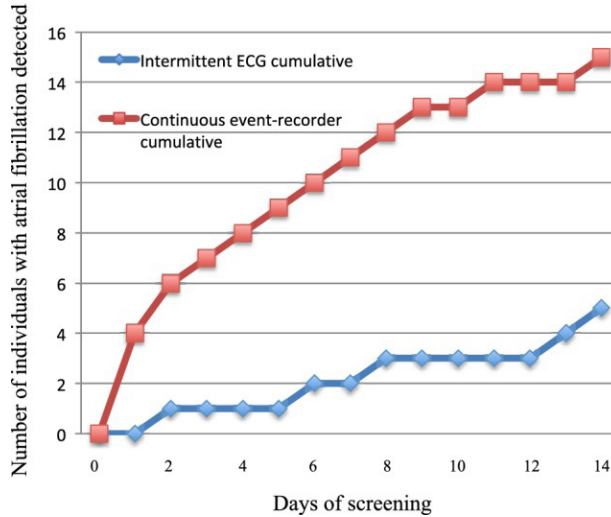

Figure 12. Time until detection of first episode of AF using intermittent ECG recordings and continuous event-recording. Reprinted courtesy of Clinical Cardiology: https:// doi.org/ 10.1002/ clc.23323 Clinical Cardiology published by Wiley Periodicals, Inc.©

In this study AF detection was three-times higher using continuous event-recording compared to intermittent ECG, which is similar to 2.5-times in study I. With regards to detection of other significant arrhythmias, the detection rates were generally higher for continuous event-recording. In total, 35 participants were referred for further investigation due to arrhythmia findings other than AF.

The algorithm used for detection of AF on intermittent ECGs did not miss any suspected episodes of AF found by manual interpretation. For continuous event-recording, 27% of the episodes verified as AF after manual interpretation were categorized by the algorithm as other arrhythmias. This led to a need for interpretation of all episodes categorised as arrhythmia by the continuous event-recorder, with an interpretation burden per participant of 55 (IQR 40-70) ECGs. For intermittent ECG, only episodes marked as suspicious AF by the algorithm needed manual interpretation. The interpretation burden for intermittent device was 3 (IQR 1-8) ECGs.

Participants were instructed to make a minimum of 56 intermittent ECGs and did 55 (IQR 40-70), 98% of expected. They were instructed to wear the continuous event-recorder for 14 days and were monitored to have done so for 13.3 (IQR 11.8-13.9) days, 94% of the expected time. Presence of palpitation symptoms did not affect compliance, neither for intermittent ECG (p=0.559) nor for continuous event-recording (p=0.804).
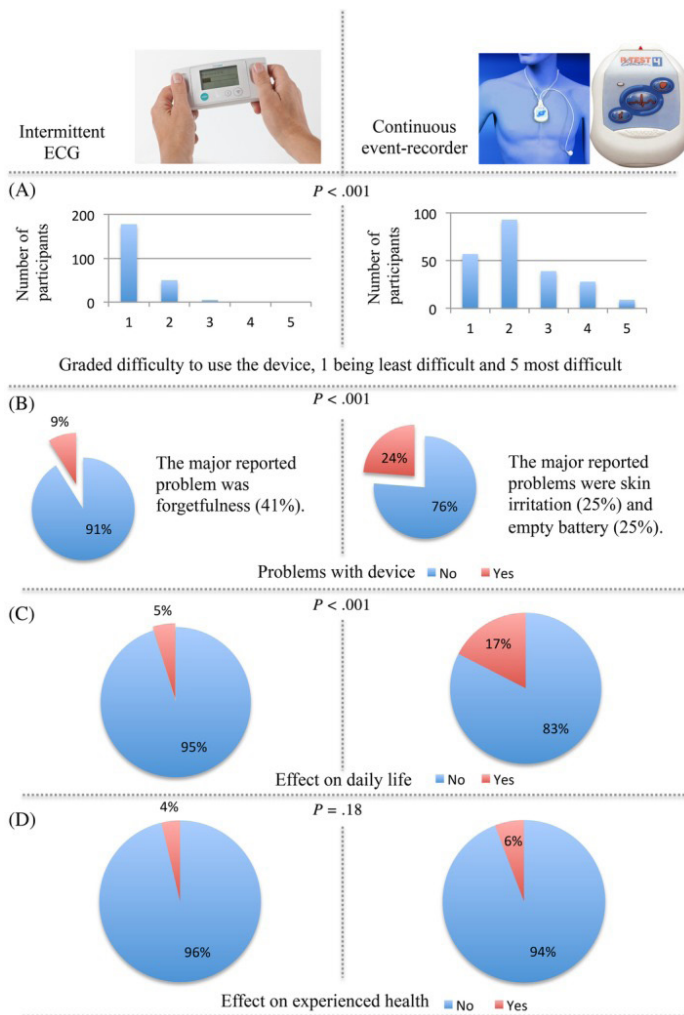

Figure 13. Results from forms completed by the participants regarding use of the two different screening devices. Reprinted courtesy of Clinical Cardiology: https://doi.org/ 10.1002/clc.23323 Clinical Cardiology published by Wiley Periodicals, Inc.©

The participants preferred the intermittent ECG screening method with regards to nearly all comparisons (see figure 13).

6.4   Study IV

Out of 6,289 participants free from AF in STROKESTOP I, 6,100 were included in this study. They had performed a median of 29 (CI 22.5-35.5) ECGs each. Of those participants, 15% had supraventricular arrhythmias (see table 4).

Variable	No arrhyth-mia	Frequent SVEBs (isolated or in bigemini/ trigemnini)	Regular SVT with p-waves	Irregular SVT with p-waves	Regular SVT without p-waves	Irregular SVT without p-waves (Micro-AF)
Number of par-ticipants	5,206	709	48	39	1	97

Table 4. Number of participants with each type of supraventricular arrhythmia. SVEBs indicate supraventricular ectopic beats. SVT indicates supraventricular tachycardia.

Median time to follow-up in registers was 4.2 (IQR 3.8-4.4) years. During follow-up 387 participants had received an AF diagnosis, 161 had suffered from stroke and 354 had died. The group with highest cumulative incidence of AF was the micro-AF group, with an incidence of nearly 20%.
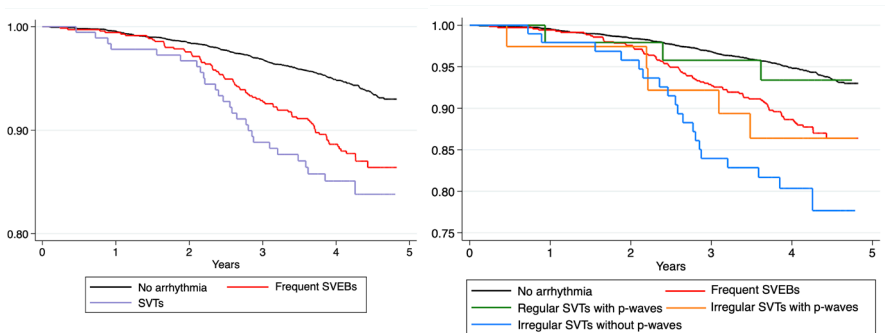

Figure 14. Kaplan-Meier curves showing primary end-point event rate (atrial fibrillation) in participants with different arrhythmias.

After adjustments for potential confounders, frequent SVEBs (including isolated, bigeminal or trigeminal) were associated with a hazard ratio of 2.1 (CI 1.6-2.7) for AF, and presence of any SVT was associated with a hazard ratio of 3.1 (CI 2.1-4.6) for AF (see figure 14). Of SVTs with different characteristics, micro-AF was shown to be the strongest predictor for AF with a hazard ratio

of 4.3 (CI 2.7-6.8), even after multivariable adjustments. The study was not powered to evaluate the risk for stroke and there was no significant increase seen. However, the risk of death was increased for individuals with micro-AF, hazard ratio 2.0 (1.1-3.8), after adjustments for potential confounders.

Most participants classified in the SVT-groups had SVTs with short duration, 7 (IQR 6-12) beats, and most participants had only one SVT episode, 1 (IQR 1-2). SVT burden did, however, did not remain a significant factor for development of AF in multivariable analysis.

7   GENERAL DISCUSSION

7.1   Major findings

In the first pilot-study that evaluated micro-AF during intermittent ECGs as a predictor for future AF, we showed that individuals with micro-AF have a five-fold increased risk of AF after two years. Nearly 80% of individuals with micro-AF that were diagnosed with AF were not diagnosed before repeat screening.

The second study was also an investigation of micro-AF seen during intermittent ECGs in elderly individuals. By extended screening with a three-month delay, AF was shown to be four-times more common in individuals with micro-AF in comparison to individuals without the finding.

In the third study, an ambulatory elderly population was screened using intermittent ECG and continuous event-recording in parallel for two weeks. Intermittent ECG was considered user-friendlier than continuous event-recording, but compliance with both screening methods was good. Three-times more new cases of AF were detected using continuous event-recording compared to intermittent ECG.

The fourth study was a comparison of prognosis in elderly individuals with different kinds of supraventricular activity seen during intermittent ECG. SVTs were shown to be a stronger predictor of future clinical AF than SVEBs. Of the SVTs, micro-AF stood out as the strongest predictor for a future clinical AF diagnosis and was also associated with an increased risk of death. After four years of follow-up, clinically diagnosed AF was four-times more common in the micro-AF group compared to the non-arrhythmia group.

With extended screening after three months in study II, 13% of participants with micro-AF were diagnosed with AF, compared to 50% after two years in study I. Only 5% had clinically detected AF before repeat screening, after two years in study II. After four years 20% of participants with micro-AF were clinically diagnosed with AF in study IV. This indicate that micro-AF can probably be both interpreted as a signal for unknown AF and a preliminary stage to AF, as the prevalence seems to increase over time. The detection of AF in elderly individuals with micro-AF can be delayed and the diagnosis may even be undiscovered if screening is not practiced. Extended and repeat screening for AF could be recommended elderly individuals with micro-AF as a finding of AF in most cases would lead to initiation of OAC. A long-time continuous screening method is preferable in such a high-risk population.

7.2 Different types of supraventricular activity

In study IV, SVTs were shown to be associated with a three-times increase in risk of AF and in participants with frequent SVEBs, the risk was doubled compared to in the non-arrhythmia group. There were no significant differences with regards to stroke or all-cause mortality comparing these groups. In a study by Johnson et al., no difference in prognostic significance was found between frequent SVEBs and SVTs (74). Other studies have focused mainly on analysing excessive supraventricular activity as a combined variable independent of classification (79).

In study IV micro-AF was shown to be associated with a four-fold increase in risk of clinically detected AF while irregular SVTs with p-waves were associated with a three-fold increased risk. The risk increase was not significant in individuals with regular SVTs with p-waves. Our study was not powered to compare differences in stroke risk and all-cause mortality, but individuals with micro-AF had a doubled risk of death. Similar results were found in a study by Johnson et al.; micro-AF was shown to be associated with a five-fold increase in risk of clinically detected AF while irregular SVTs with p-waves were associated with a three-fold increase. They identified more episodes of regular SVTs without p-waves than we did. Interestingly, these episodes were associated with a three-fold increase in risk of AF and were the only supraventricular arrhythmia associated with stroke, with a 14-fold increased risk (84).

In study II, using extended screening, individuals with micro-AF were shown to have an absolute risk of earlier undetected AF of 13%. The risk of screening detected AF within three months in individuals with micro-AF is 65% of having it clinically detected after four years (13% divided by 20%). If this known relationship is extracted to other arrhythmias in study IV, 7% of individuals with frequent supraventricular ectopic beats would have had AF detected by repeat screening within three months, and 10% of participants with SVTs independent of characteristics would have had AF detected. One can hypothesise that these groups may also benefit from extended AF screening. We do not know, however, if the development of AF in these individuals with other arrhythmias follows the curve of micro-AF patients.

An association with general prothrombotic atrial myopathy may explain the increased risk of AF and stroke seen in individuals with short SVTs with AF characteristics in comparison to patients with other atrial tachycardias. The increased risk of stroke in patients diagnosed with AF is thought to be explained, at least partly, by atrial myopathy (32). Regular SVTs like ectopic atrial tachycardia, atrial flutter and atrioventricular nodal re-entry tachycardias are caused by smaller focal atrial defects (102) and are not necessarily associated with general atrial myopathy. Although, non-classified SVTs are to some extent associated with an elevated risk of stroke (103).

7.3 Stroke risk in atrial fibrillation with varying duration and symptoms

It has frequently been discussed whether or not screening detected AF is associated with the same stroke risk as clinically diagnosed AF, as participants with screening detected AF are thought to have less symptoms and a lower AF burden (104). In study II, 15% reported typical AF symptoms during their participation in the study, but no-one reported AF symptoms at the exact time when AF was seen during the recording. As the study populations were the same, neither did participants diagnosed with AF in study III report symptoms at the time of the event. The total AF burden in participants diagnosed with AF in study II and III was 1-2% during two-weeks continuous event-recording (105).

Asymptomatic AF is associated with an increase in stroke risk and all-cause mortality compared to no AF (63, 86). A meta-analysis including six different studies of individuals with symptomatic and asymptomatic AF found no difference in stroke rate or all-cause mortality. It concluded that presence of symptoms should not determine the treatment approach (62).

The CHA_2DS_2VASc score system has not been validated for use in determination of OAC treatment in patients diagnosed with AF during long-term ECG recording (106). According to a meta-analysis that includes 12 studies (107), long-standing AF is associated with a higher risk of stroke when compared to paroxysmal AF. However, it is unknown if the increase in stroke risk may be related to increased prevalence of co-morbidities. Paroxysmal AF is still associated with an increased risk of stroke and often progresses to non-paroxysmal forms (108). Also, OAC treatment in individuals with high CHA_2DS_2VASc scores has been shown, independent of AF diagnosis, to be beneficial (31). AF burden may therefore only be of importance for individuals with a low underlying risk of stroke, men with CHA_2DS_2VASc score 1 and women with CHA_2DS_2VASc score 2 (13). In our studies all participants diagnosed with AF had indication for OAC treatment as their median score was 3 (3-4).

It remains to be investigated if individuals with screening-detected AF have the same risk of stroke as asymptomatic patients with low AF burden. According to ESC guidelines, ECG-verified screening-detected AF is treated in the same way as clinically diagnosed AF. It is not recommended to take AF burden and symptoms into account (13). All participants included in our studies with AF lasting for at least 30 seconds were initiated on OAC treatment.

7.4   Screening in specific risk groups

AF is a common disease, affecting at least 3% of the adult population in Sweden (2). The prevalence is expected to double within 50 years from now (5, 6). AF is associated with a five-fold increase in stroke risk and a doubled risk of death (13, 15). The risk of stroke in AF patients decreases at least 64% using OAC compared to placebo (39). Among patients with AF, about one third are thought to be asymptomatic and 25% have paroxysmal AF (109, 110). AF is therefore difficult to diagnose and an under-diagnosed condition (9). Stroke can be the first manifestation of AF; in 10% of people diagnosed with stroke AF is detected first at the time of the event (111). These factors together have made screening for AF a subject of interest in an effort to increase AF detection and offer early OAC treatment.

Several strategies have been tested to try to reduce the numbers needed to screen and still detect AF in those with high risk of stroke. For patients with confirmed stroke or TIA, ESC guidelines already recommend screening for AF (13).

The prevalence of AF increases steeply with age (3). AF detection is very low in individuals aged <65 years (47). Age is also one of the strongest predictors for stroke in AF patients (112). According to ESC guidelines systematic screening for AF may be considered in individuals >75 years of age or those at high risk of stroke (13).

CHA_2DS_2-VASc score is commonly used to predict stroke risk in AF patients but can also be used to identify individuals with an increased risk of having AF (113).

NT-proBNP is one of the strongest predictors for AF (114) and is also associated with an increased risk of stroke in AF patients (115). In the population-based screening study for AF, STROKESTOP I, all participants randomised to screening did intermittent ECG recordings for two weeks. In STROKESTOP II all participants randomised to screening did an index ECG, but only participants with elevated levels of NT-proBNP did intermittent recordings for two weeks. On index ECG a markedly higher proportion of participants with elevated NT-proBNP were diagnosed with AF compared to the low-risk group, indicating that NT-proBNP is usable as a discriminative biomarker. Also, a similar proportion of newly detected AF was found in the two screening studies, despite that the number of participants performing two-weeks intermittent ECG was reduced by 41% in STROKESTOP II (9, 116).

In our studies micro-AF seems to be a remarkably strong predictor for AF and also a predictor for death. An earlier study has shown that the stroke risk in individuals with excessive supraventricular activity and CHA_2DS_2-VASc -score ≥ 2 is comparable to the stroke risk in AF patients, 2.4 % per year (82). Selection of screening populations based on variables both associated with an increased risk of AF and stroke is optimal. The difficulty

with use of micro-AF for guidance of whom to screen is that a first screening step is needed to detect micro-AF. Despite this difficulty it is a valuable source of guidance of who to screen repeatedly and more extensively.

7.5   Population-based screening

Opportunistic screening for AF by pulse palpation or single ECG strip is recommended in individuals >65 years (13). There are several ongoing large-scale screening studies from which long-term data with regards to hard endpoints will be available. The results of these studies may help to determine if the stroke risk in screening detected AF is similar to the risk in clinically diagnosed AF and if a systematic nation-wide screening program for AF could be cost-effective and life-saving (104). One suggested age for population screening is 75 years, as current ESC guidelines recommend OAC treatment in individuals ≥75 years old with AF regardless of co-morbidities (13). In addition, a simulation study has concluded that screening at the age of 75 may result in the lowest cost per quality-adjusted life-year gained (117).

Non-participants in AF screening studies have been shown to have more co-morbidities and higher incidence of stroke than participants (118). The non-participants are probably also more likely to have AF. Rates of attendance to screening programs are also affected by socio-economic status (119, 120). In STROKESTOP I non-participants had lower education, lower income levels and were more commonly immigrants (121). Travel distance to screening centres also affected participation and is probably more likely to affect participation in high-risk individuals. Not reaching out to the most vulnerable groups can potentially lead to under-diagnosis and under-estimation AF prevalence. Easy access to screening centres and information available in different languages might be important in study design.

The optimal choice of screening method may depend on the population screened, their risk of AF and stroke. In study III we saw that intermittent ECG detected a significant number of new AF cases in an elderly population (2%), but detection using continuous event-recording for the same period of time was three-times higher (6%). Both screening devices were well-tolerated in an elderly population, but participants liked the intermittent ECG better.

The yield of AF, of course, depends a lot on the underlying prevalence in the population screened and the screening method. In the REHEARSE-AF study the prevalence of screening detected AF was found to be 3% as in STROKESTOP I and II. The participants had a mean age of 72.6 years and CHA_2DS_2VASc score of 3. They did intermittent ECGs using the AliveCor Kardia system twice per week for a year (122). A considerably higher prevalence of new AF was detected in the ASSERT-II study including participants with a mean age of 74 years and CHA_2DS_2VASc score of 4.1. Implantable

subcutaneous ECG monitoring was used for screening. After 1.3 years 34% of participants were diagnosed with AF (86). In the REHEARSE-AF study, an episode of AF-activity had to last at least 30 seconds for diagnosis. In the ASSERT-II study, an episode had to last for at least five minutes to be included.

A multi-step approach to screening may be optimal for high yield of AF detection, but still to a lower cost and need of less resources. In STROKESTOP II all participants did an index ECG, only participants with NT-proBNP ≥125 ng/L were screened with intermittent ECG for two weeks (116). Still, the total prevalence of newly detected AF in participants randomised to screening in STROKESTOP II was similar to that found in STROKESTOP I. After extended screening in participants with micro-AF in STROKESTOP II the AF prevalence was increased by 22%, with only 200 participants more extensively investigated. Intermittent ECG could possibly also be replaced by more extensive screening using a continuous device in known high-risk participants at inclusion, for example with CHA_2DS_2-VASc score >3 in men and >4 in women or NT-proBNP above a certain level.

In STROKESTOP II individuals with NT-proBNP ≥900 ng/L were considered to have high risk of having heart failure and were referred to echocardiography (123). This cut-off level could possibly also be used to identify individuals with an increased risk of AF where prolonged screening might be of value as the diseases are often seen together. Individuals with NT-proBNP ≥ 290 ng/L have compared to ≤ 51 ng/L, been shown to have a four-fold increase in risk of clinically detected AF after adjustments for potential confounders (114).

7.6   Primary prevention for atrial fibrillation

For individuals with micro-AF and for whom OAC is not yet known to be effective, primary and secondary prevention of AF can be of interest (14). The same actions may also decrease the supraventricular burden and atrial myopathy. Management of adjustable risk factors such as hypertension, diabetes mellitus, sleep apnoea, physical inactivity and obesity may prevent progression from micro-AF to AF.

An elevated risk for AF has been seen in individuals with poorly controlled blood pressure (124). Some of the hypertension treatments have been shown to reduce AF recurrence and burden (14). In our study participants seemed to have well-regulated blood pressure, and hypertension was not found to be more common in participants with micro-AF and AF.

Individuals diagnosed with diabetes mellitus seem to have a 40% higher risk of AF, and that risk is associated with poor glycaemic control. Participants with micro-AF did not have a higher prevalence of diabetes mellitus in our studies, but we do not have access to information regarding blood sugar regulation. AF was also not more commonly diagnosed in our study participants with diabetes mellitus.

Observational studies have shown an association between sleep apnoea severity and incidence as well as burden of AF (14). Individuals with AF and sleep apnoea using CPAP seem less likely to develop more permanent forms of AF (125).

Physical inactivity seems to independently affect the AF burden, not only depending on comorbidities. Physical activity may reduce the risk of new onset AF (14). Extreme physical activity, however, like marathon running, is associated with a nearly nine-fold increase in risk of AF (126).

Obesity is a strong risk factor for AF and seems to affect both development of disease and AF burden (14). It is known that weight loss ≥10% in obese individuals diagnosed with AF is associated with a six-times longer arrhythmia-free survival rate (127). Most participants in our studies both with micro-AF and AF had a BMI of around 25.

To reduce the risk for AF and reduce the AF burden it is recommendable to strive for BMI ≤25 kilograms/meter² and to incrementally increase physical exercise up to the moderate-intense level with a duration of 200 minutes per week. Smartphones and dietary apps that can provide feedback to users are suggested to facilitate these goals. Another alternative is weight loss programs. Blood sugar control in diabetes patients as well as well-treated hypertension may also be beneficial. Screening for sleep apnoea and CPAP treatment when indicated is also recommended (14). These recommendations may be beneficial, even for individuals with micro-AF.

7.7   Limitations

The knowledge about micro-AF from the studies included in this thesis is limited to an elderly population and most participants were Caucasian. This may affect the external validity. Another study, however, of younger participants (mean age of 64.5 years) with irregular SVTs showed similar results (84). All study participants were recruited from STROKESTOP I and II. It is possible that individuals participating in these screening studies were healthier than the general population (128). Participants in screening might also be more highly motivated than the general population. In study III, compliance to both screening devices was high, particularly to continuous event-recording that was considered less user-friendly, compliance could be assumed to be lower in a real-world setting.

AF is more common in individuals with increased levels of NT-proBNP (114). The participants in study II and III all had elevated NT-proBNP levels. The AF prevalence found in these studies may not be representative of the general population. Subsequently, micro-AF prevalence in study II may also have been overestimated. It is possible that micro-AF is a stronger predictor for AF in individuals with elevated NT-proBNP. As participants in study III were their own controls, this did not affect the comparison.

Our studies have covered extensive but still limited screening for AF at two specific time-points – after three months and two years. AF cases may thus have remained undetected. To really know the progression rate from micro-AF to AF, years of internal loop-recording may be needed. By use of registry diagnosis in study IV, subclinical cases of AF and stroke cannot be accounted for leading to weakening of the statistical associations.

Participants in STROKESTOP I were screened using intermittent ECG, it is unknown how much AF would have been detected if continuous event-recording would have been used instead. This makes it difficult to conclude from study I if micro-AF should be considered a sign of undetected AF or a preliminary stage to AF. The AF prevalence found in individuals with micro-AF, however, was significantly higher in study I after two years compared to in study II, after three months. In study II the micro-AF group underwent extended AF screening three months later than the control group. More cases of AF may have been found in the control group using the same time to follow-up. This may have caused an overestimation of our findings.

From our studies we cannot draw any conclusions regarding importance of micro-AF burden. Although there were significant differences in duration and number of micro-AF episodes between individuals diagnosed with AF and those who were not, the differences did not remain significant in multivariable comparisons. Neither were our studies powered to evaluate the stroke risk in individuals with supraventricular arrhythmia. The results may have been different with a prolonged time to follow-up.

Both the intermittent ECG and the continuous event-recorder are one-lead devices. P-wave analyses were sometimes difficult; especially atrial flutter may have been missed. This introduces a risk of misclassification bias. From R-Test 4 full disclosure ECGs were not available for all suspicious AF episodes. Due to memory and storage limitations, not all episodes of suspected arrhythmia were stored. This made it difficult to determine the AF burden. As the device has a propensity to over-diagnose AF, manual inspection of the stored episodes was needed to diagnose AF. Some cases may have been missed due to limited storing capacity of the device.

With the diagnostic criteria used for micro-AF within study I, an episode was difficult to identify, as it was short and not necessarily tachycardia. There is a risk that different types of supraventricular activity were classified the same. Therefore, to make the finding easier to identify in clinical practice, we decided to prolong the needed duration and added the tachycardia criteria to micro-AF diagnostics.

The researchers were not blinded in study I and II. During ECG interpretation it was known to which group the participants belonged, which could have caused bias.

8 CONCLUSIONS

Micro-AF is found in 2% of an unselected 75-76 year old population and in 6% of individuals with the same age and increased levels of NT-proBNP, using intermittent ECG. Elderly individuals with micro-AF seen during intermittent ECG have a four-five-fold increase in risk of both undetected and future AF compared to a control group. With a four-fold increase in AF prevalence after two years compared to after three months, the prevalence of AF seems to steeply increase over time in this group. Relation between micro-AF burden and AF development did not remain significant after multivariable adjustments.

Extended and repeat screening for AF could be recommended given that a finding of AF in most cases would lead to initiation of OAC. In an ambulatory elderly population, intermittent ECG is more acceptable than continuous event-recording. Continuous event-recording, however, detects three-times as many new cases of AF compared to intermittent ECG when they are applied in parallel for two weeks. Accordingly, in a high-risk population, continuous event-recording albeit more time-consuming is the preferable choice of screening method due to higher AF detection rates than intermittent ECG.

All kinds of extensive supraventricular activity seem to be associated with an increased risk of AF, although more organized atrial arrhythmic episodes are increasingly associated with AF development. Individuals having SVTs with AF characteristics – micro-AF – have a higher risk of a future clinical AF diagnosis than patients with other supraventricular activity. Micro-AF is also associated with an increased risk of death, but no significant increase in risk of stroke was found.

9 CLINICAL IMPLICATIONS

According to the present guidelines for AF, the definition of AF is an irregular heart rhythm without p-waves lasting a minimum of 30 seconds, a duration based on expert consensus rather than scientific data. Some earlier studies have already displayed a linkage between short episodes of AF-like activity and development of AF and stroke. An early diagnosis of AF and initiation of treatment with oral anticoagulants might lead to a significant reduction of the risk of a stroke in high-risk individuals. AF is often paroxysmal and asymptomatic which leads to diagnostic difficulties. Considering this, identification of risk factors for having or developing AF is important. It has been shown that micro-AF can be both a sign of an already existing AF and have a rapid progression rate to AF. A standardised follow-up could therefore be recommended. This follow-up may lead to earlier AF diagnosis, risk-factor modification and might potentially reduce stroke risk in an elderly population.

10   FUTURE PERSPECTIVE

Primary preventive systematic screening for AF has not yet been shown to have an impact on the societal stroke burden or to be cost-effective. It is not known if AF cases detected by screening have the same beneficial effect of OAC as symptomatic cases. Although, it is known that they have an increased risk of stroke compared to the general population. Individuals with screening detected AF may also have less AF burden than individuals with clinically diagnosed AF. Whether or not the burden affects the stroke risk is still not fully known. Ongoing studies are evaluating the potential benefits of OAC in individuals with AHRE seen during long-term recording and may answer this question. Five-year follow-up data from the AF screening study STROKESTOP I and long-term data from several other large randomised controlled screening studies will soon be available and may affect the recommendations regarding screening for AF.

Different strategies for targeting only high-risk individuals with screening to reduce costs are discussed. As an effort to reduce the screening burden in the STROKESTOP II screening study, only individuals with increased levels of NT-proBNP, who were believed to have the highest risk of AF and stroke, were screened extensively. The studies included in this thesis indicate that micro-AF could also be used for guidance with regards to which individuals with increased levels of NT-proBNP would benefit from even more extensive screening.

It is still difficult to choose one optimal screening method for AF in high-risk populations. We know that continuous methods used during long time periods detect more AF than intermittent ECG. The problems with skin irritation caused by the sticky patches used to apply continuous ECG must be solved. A continuous screening method that has good signal quality without using patches may eventually develop. That kind of a device would probably be optimal for use in high-risk individuals. Different wearable devices are now available also for use as self-screening. However, these devices, similar to most screening programs, tend to attract young and healthy individuals with low risk of both AF and stroke. We need strategies to direct screening towards the groups that will benefit most from participation in it.

The mechanism that leads to increased stroke risk in AF patients is still unknown. The risk increase has been explained for a long time to be due to changes in movement patterns of the atrium during AF. On the other hand, there are results that indicate that individuals diagnosed with AF are at increased risk of stroke even during long periods of sinus rhythm. One possible explanation for this phenomenon could be that AF may actually be a sign of prothrombotic atrial myopathy that leads to electrical disturbances. If that is true, short episodes of AF-like activity could potentially be seen as signs of atrial myopathy. This may explain the results of register

studies in which individuals with really short episodes of AF-like activity have been shown to have an increased risk of stroke. Further research is needed to clarify if episodes of AF-like activity shorter than 30 seconds may merit OAC treatment.

The association between AF and dementia seen in register studies has been discussed a lot lately. The relationship may be explained by silent infarcts and vascular lesions caused by micro-embolism. There are no results available with regards to risk of dementia in patients with excessive supraventricular activity. An increased risk of dementia in individuals with micro-AF would potentially motivate initiation of OAC treatment as well. As dementia related to AF is thought to be a continuous disease rather than being dichotomous like stroke, OAC treatment may also be of value in individuals with lower CHA_2DS_2-VASc scores.

More studies are required to answer these important questions regarding who could benefit from OAC treatment. It would be interesting to perform a prospective study of micro-AF patients equipped with internal loop-recorders to determine the role of AF burden and timing in relation to stroke and dementia. In the future it would also be interesting to perform a trial using stroke as primary endpoint and major adverse event as secondary endpoints, randomising individuals with micro-AF and high CHA_2DS_2-VASc scores to OAC or no treatment.

11   SVENSK SAMMANFATTNING

11.1   Bakgrund

Förmaksflimmer är den vanligaste hjärtrytmrubbningen av klinisk relevans. Eftersom förmaksflimmer förekommer i högre utsträckning hos äldre och befolkningen är åldrande beräknas sjukdomsprevalensen komma att öka. Livstidsrisken för att insjukna beräknas till 25 % för medelålders personer idag. Obehandlat förmaksflimmer innebär en kraftigt ökad risk för stroke hos de flesta individer. Strokeinsjuknanden som orsakas av förmaksflimmer är förknippade med högre mortalitet och morbiditet än stroke på grund av andra orsaker. Blodförtunnande behandling är indicerad för de flesta patienterna med förmaksflimmer och minskar risken för insjuknande i stroke med nästan 70 %. En tredjedel av patienterna med förmaksflimmer har inga symtom och en fjärdedel har endast intermittenta arytmiepisoder. De har trots detta en lika hög risk för insjuknande i stroke.

Eftersom diagnosen förmaksflimmer kräver EKG görs ofta längre EKG-registreringar för att leta efter förmaksflimmer och i flera studier används systematisk screening för förmaksflimmer. Ett exempel på en systematisk mass-screeningstudie för förmaksflimmer är STROKESTOP I, där 75- och 76-åringar i Stockholms- och Hallands län screenades för förmaksflimmer med hjälp av intermittent EKG 30 sekunder två gånger dagligen i två veckor. Senare har även STROKESTOP II-studien genomförts. Genomförandet liknar genomförandet i STROKESTOP I. Däremot inkluderades endast deltagare från Stockholms län och endast individer med NT-proBNP ≥125 ng/L fick genomgå extensiv förmaksflimmerscreening. Deltagarna instruerades att göra 30 sekunders intermittent EKG-registrering fyra gånger dagligen istället för två gånger dagligen, i två veckor.

För att en episod av oregelbunden hjärtrytm ska räknas som förmaksflimmer ska den enligt konsensus vara minst 30 sekunder lång. I samband med längre EKG-registreringar och systematisk screening för förmaksflimmer ses ofta kortare hjärtrytmrubbningar, ihållande förmaksarytmier och enstaka förmaksutlöst extraslag. Dessa har i registerstudier visats vara förknippade med en ökad risk för förmaksflimmer och även en ökad risk för stroke. I klinisk praxis anses korta episoder av förmaksflimmerliknande aktivitet fortfarande oftast som ofarliga. Patienter med dessa arytmier erbjuds för närvarande ingen uppföljning eller behandling, trots att de har en ökad risk för både förmaksflimmer och stroke.

Förmaksarytmier kan ha olika karakteristika och anses vara förknippade med olika risker. I denna avhandling har vi främst fokuserat på riskerna och kliniska implikationer vid ihållande förmaksarytmier som liknar förmaksflimmer, men som är kortare 30 sekunder och därmed ej uppfyller diagnoskriterierna för förmaksflimmer. Dessa episoder benämner vi mikroflimmer. I studie I definieras mikroflimmer som episoder av ≥4 efterföl-

jande förmaksutlösta extraslag, oregelbunden rytm, avsaknad av p-vågor och med duration <30 sekunder. I studie II-IV definieras mikroflimmer som episoder av ≥5 efterföljande förmaksutlösta extraslag, hjärtfrekvens >100 slag/minut, oregelbunden rytm, avsaknad av p-vågor och med duration <30 sekunder. Det finns många olika utrustningar som används för förlängda EKG-registreringar. I våra studier har vi använt tum-EKG från Zenicor som intermittent EKG och R-test 4 från Novacor för kontinuerlig event-recording.

11.2 Syfte

I pilot-studien, studie I, var syftet att undersöka om mikroflimmer utgör en risk för senare utvecklande av förmaksflimmer genom upprepad screening. Vi ville även jämföra förmaksflimmerdetektionen mellan kontinuerlig event-recording och intermittent EKG. Syftet med studie II var att undersöka om mikroflimmer kan användas som en indikator för oupptäckt förmaksflimmer, genom utvidgad screening. Studie III syftade till att i ett större material än i studie I, jämföra förmaksflimmerdetektionen mellan kontinuerlig event-recording och intermittent EKG i en äldre population, men även jämföra följsamhet i utredning och användarvänlighet hos EKG-utrustningarna. I den sista studien, studie IV, ville vi ta reda på förekomsten och betydelsen av olika förmaksutlösta arytmier i en äldre population. Vi ville även jämföra hur stor andel av deltagarna med respektive arytmi som senare fick kliniskt diagnostiserat förmaksflimmer eller drabbades av stroke, samt deras mortalitet via registeruppföljning.

11.3 Metod och Resultat

I studie I inkluderades, n=102, deltagare från en subpopulation i STROKESTOP I-studien. Deltagarna delades in i två grupper beroende på resultatet från deras intermittenta EKG-registreringar i STROKESTOP I: en mikroflimmergrupp, n= 54, och en matchad kontrollgrupp, n=48. Efter två års uppföljningstid bjöds deltagarna som inte kliniskt diagnosticerats med förmaksflimmer in till upprepad förmaksflimmerscreening under två veckors tid. De screenades med en kontinuerlig event-recorder och intermittent EKG parallellt i två veckor. Efter en median-uppföljningstid på 2,3 år visades sig 50 % av deltagarna med mikroflimmer ha utvecklat förmaksflimmer jämfört med 10 % i kontrollgruppen, p <0,001. Av de nydiagnostiserade fallen med förmaksflimmer hittades 40 % (n=10/25) med intermittent EKG jämfört med 100 % (n=25/25) med kontinuerlig event-recording, p <0,001.

I studie II inbjöds deltagare från STROKESTOP II-studien där intermittent EKG visat mikroflimmer, snarast möjligt efter sitt deltagande, till utvidgad förmaksflimmerscreening med kontinuerlig event-recorder i två veckor. En kontrollgrupp i STROKESTOP II-studien utan mikroflimmer screenades med båda EKG-metoderna parallellt. Av de 3763 deltagarna

i STROKESTOP II-studien, med förhöjt NT-proBNP och utan tidigare förmaksflimmerdiagnos, hade 225 (6%) mikroflimmer. Av dessa var 200 villiga att delta i utvidgad screening med kontinuerlig event-recorder. Förmaksflimmer hittades hos 13 % i mikroflimmergruppen jämfört med 3 % i kontrollgruppen, p <0,001.

Studie III utgår från kontrollgruppen i studie II. Alla deltagare i kontrollgruppen var vid studiestart fria från känd förmaksflimmerdiagnos och screenades för förmaksflimmer med hjälp av två olika EKG-utrustningar. De instruerades att registrera intermittent EKG 30 sekunder fyra gånger dagligen i två veckor samt att bära kontinuerlig event-recorder parallellt. Båda utrustningarna kunde manuellt aktiveras för EKG-inspelning vid symtom. Deltagarna ombads även att fylla i ett formulär med jämförande frågor gällande följsamhet till undersökning och användarvänlighet, för de två EKG-utrustningarna. Intermittent EKG diagnosticerade förmaksflimmer hos 2 % (n=5/269) och kontinuelig event-recording hittade förmaksflimmer hos 6 % (n=15/269), p = 0,002. Ingen deltagare diagnosticerades enbart med intermittent EKG. På en skala mellan 1 och 5, där 1 motsvarade väldigt lätt att använda, graderades användarvänligheten för intermittent EKG enligt följande 1 (interquartile range [IQR]: 1–1) och för kontinuerlig event-recording till 2 (IQR: 1–3), p <0,001.

Mikroflimmer eftersöktes bara hos deltagare under sista månaderna av inklusion i STROKESTOP I, därför ingår endast en liten andel av deltagarna med mikroflimmer i studie I. En datoriserad algoritm användes i studie IV för att hitta fler deltagare med förmaksarytmier i STROKESTOP I. Alla episoder som identifierades av algoritmen granskades även manuellt. Det primära utfallsmåttet var kliniskt diagnostiserat förmaksflimmer (register-diagnos), sekundära utfallsmått var stroke och död. Uppföljningstiden var 4,2 (IQR: 3,8–4,4) år. Av de 6100 deltagarna hade 15 % förmaksarytmier av betydelse. Deltagarna med arytmier delades in i grupper beroende på typ av förmaksarytmi. Ihållande förmaksarytmier visade sig vara starkare associerade med förmaksflimmer än enskilda extraslag. Deltagarna med mikroflimmer, n= 97 (1,6 %) hade betydligt högre risk för förmaksflimmer (hazard ratio 4,3; 95 % konfidens intervall 2,7–6,8) än personer med andra typer av ihållande hjärtklappningar. De hade också en ökad risk för död (hazard ratio 2,0; 95 % konfidens intervall 1,1–3,8).

11.4 Slutsatser

Förekomsten av kliniskt signifikanta förmaksarytmier i åldersgruppen 75–76 år är ungefär 15 % och förekomsten av mikroflimmer är minst 1,6–6 %. Det finns flera olika typer av ihållande förmaksarytmier, av dessa är mikroflimmer, som i sin elektriska aktivitet är mest likt förmaksflimmer också starkast associerat med förmaksflimmer.

Mikroflimmer tycks kunna vara både en markör för att odiagnostiserat förmaksflimmer kan finnas, men även ett förstadium till förmaksflimmer. Med kort uppföljningstid (3 månader) till utvidgad förmaksflimmerscreening diagnosticerades 13 % av deltagare med mikroflimmer med förmaksflimmer, jämfört med 50 % efter 2 år. Äldre individer med mikroflimmer har också en ökad risk för död.

Betydligt färre fall av förmaksflimmer diagnostiseras kliniskt hos personer med mikroflimmer jämfört med vid upprepad screening i denna högriskgrupp. Kontinuerlig event-recording hittar tre gånger så många nya fall av förmaksflimmer som intermittent EKG i en äldre population, även om följsamheten och användarvänligheten skattas högre för intermittent EKG. Utvidgad och upprepad förmaksflimmerscreening med kontinuerligt EKG är att rekommendera hos individer med mikroflimmer för att tidigt diagnosticera förmaksflimmer och därmed sannolikt minska risken för stroke.

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