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SCREENING FOR ATRIAL FIBRILLATION AND TREATMENT WITH ANTICOAGULANT TO PREVENT STROKE

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SCREENING FOR ATRIAL FIBRILLATION AND TREATMENT WITH ANTICOAGULANT TO PREVENT STROKE

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*“Though the prophet's word may come to an end, tongues come to nothing,
and knowledge have no more value, love has no end”*

Bible, 1 Corinthians 13:8

I would like to praise and thank GOD for helping me do this work and
supporting me throughout my life.

I dedicate this thesis to the martyrs of my ancestors who were treacherously killed in Turkey after the end of the First World War, as well as to the spirit of the martyr Lina and the spirit of my father, who was my first teacher and who wanted to see me become a doctor one day, but who died a young man.

ABSTRACT

AIMS AND METHODS

The aim of this thesis was to evaluate the outcomes of two cross-sectional screening projects for atrial fibrillation (AF) in primary care using intermittent ECG three times per day over a 2-week period. The target population in the first project were 70–74-year-old individuals registered in a single primary healthcare centre, while in the second project the target population were patients 65 years of age and older attending four different primary healthcare centres. The outcomes were the detection rates of new AF cases and the initiation rates of oral anticoagulant (OAC) treatment to prevent stroke. In the first screening project, we also investigated the roll of NT-proBNP for detecting new AF cases. In addition, we assessed the safety of the first screening project at a three-year follow-up, as well as the cost-effectiveness of the screening. Finally, we studied the validity of self-pulse palpation for detecting new AF cases in the second screening project in which the participants were instructed in how to take their own pulses simultaneously with intermittent ECG measurements.

RESULTS

Study I: The target population was invited to the screening study when visiting the primary healthcare centre over a ten-month period, while those not in contact with the centre during this ten-month period were invited to participate by letter. Of the 415 eligible individuals, 324 (78.1%) participated in the study. The mean age of the participants was 72 years and 52.2% of them were female. In the target population, 34 (8.2%) patients had previously known AF. Among participants without previously known AF, 16 (5.5%) cases of AF were detected. The final prevalence of AF in the target population was 12%. OAC therapy was initiated in 88% of the patients with newly detected AF.

Study II: Plasma NT-proBNP was measured in all patients with previously known AF, all newly detected AF and 53 participants without AF. The median NT-proBNP levels were 697 ng/L, 335 ng/L and 146 ng/L in patients with previously known AF, in patients with newly detected AF and in participants without AF, respectively. After adjustment for several clinical variables, the differences of median NT-proBNP levels were statistically significant between patients with previously known AF and patients with newly detected AF, as well as between patients with newly detected AF and those without AF. The area under the receiver operating characteristic curve for detection of new AF cases was 0.68 (95% CI 0.56 to 0.79), resulting in a cut-off point of 124 ng/L with 75% sensitivity, 45% specificity and 86% negative predictive value.

Study III: While the mortality rate among patients with known AF was higher than those with no AF (hazard ratio 3.6, 95% CI 1.5 to 8.7), there was no statistically significant difference in the mortality rate between cases of new AF compared to those cases of no AF (hazard ratio 0.86, 95% CI 0.12 to 6.44). Adherence to OAC was 92%. No stroke or severe bleeding was detected. The incremental cost-effectiveness ratio of screening vs. no screening

was EUR 2,389/QALY gained. In a probabilistic sensitivity analysis, the screening showed a 99% probability of being cost-effective compared to no screening at a willingness-to-pay threshold of EUR 20,000/Quality-Adjusted Life-Year (QALY).

Study IV: A total of 1,010 patients (mean age 73 years, 61% female) participated in the study and 27 (2.7%, 95% CI 1.8 to 3.9%) new cases of AF were detected. Anticoagulants could be initiated in 26 (96%, 95% CI 81 to 100%) of these cases. A total of 53,782 simultaneous pulse and ECG recordings were registered. AF was verified in 311 ECG recordings, of which the pulse was palpated as irregular in 77 patients (25%, 95% CI 20 to 30% sensitivity per measurement occasion). 15 out of 27 AF cases felt an irregular pulse on at least one occasion (56%, 95% CI 35 to 75% sensitivity per individual). 187 individuals without AF felt an irregular pulse on at least one occasion. These resulted in a specificity of (98%, 95% CI 98 to 98%) and (81%, 95% CI 78 to 83%) per measurement occasion and per individual, respectively.

CONCLUSIONS

The detection rate for new AF in these screening studies was 5.5% among 70–74-year olds and 2.7% among patients aged 65 years and older. Initiation of OAC was high (88% and 96%, respectively) and three-year adherence was high (92%) in the first screening study. The participation rate in the first study was high (78.1%). NT-proBNP would appear to be a useful screening marker for AF detection and AF persistence while the validity of self-pulse palpation for AF detection was low. The screening appears to be safe and cost-effective using traditional cost-effectiveness thresholds (EUR 2,389/QALY gained). Thus, opportunistic screening of AF in primary care using intermittent ECG (with or without NT-proBNP) and initiation of OAC for detected AF cases could be a suitable method for preventing stroke. However, there is a need to evaluate the efficacy of such a screening programme by a large multicentre randomized control study with stroke as the endpoint.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers (studies), which will be referred to by their Roman numerals:

- I. Ghazal F, Theobald H, Rosenqvist M, Al-Khalili F.
Feasibility and outcomes of atrial fibrillation screening using intermittent electrocardiography in a primary healthcare setting: A cross-sectional study.
PLoS One. 2018;13(5):e0198069.
- II. Ghazal F, Theobald H, Rosenqvist M, Al-Khalili F.
Assessment of N-terminal pro-B-type natriuretic peptide level in screening for atrial fibrillation in primary health care.
PLoS One. 2019;14(2):e0212974.
- III. Ghazal F, Aronsson M, Al-Khalili F, Theobald H, Rosenqvist M, Levin LÅ
Levin
Safety and cost-effectiveness of screening for atrial fibrillation in a single primary care centre at three-year follow-up.
Manuscript.
- IV. Ghazal F, Theobald H, Rosenqvist M, Al-Khalili F.
Validity of daily self-pulse palpation over two weeks for screening for atrial fibrillation among patients 65 years of age and older seeking primary care: A cross-sectional study.
PLoS Med. 2020, accepted.

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LIST OF ABBREVIATIONS

AC	Anticoagulant
AF	Atrial Fibrillation
AUC	Area Under Curve
BMI	Body Mass Index
CI	Confidence Interval
DM	Diabetes Mellitus
ECG	Electrocardiogram
ESC	European Society of Cardiology
GFR	Glomerular Filtration Rate
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
HR	Hazard Ratio
HT	Hypertension
ICER	Incremental Cost-Effectiveness Ratio
IQR	Interquartile Range
NT-proBNP	N-Terminal pro B-type Natriuretic Peptide
OAC	Oral Anticoagulants
OR	Odds Ratio
PHC	Primary Health Care
PHCC	Primary Healthcare Centre
QALY	Quality-Adjusted Life-Year

1 INTRODUCTION

1.1 DEFINITION AND CLASSIFICATION

Atrial Fibrillation (AF) is defined according to the European Society of Cardiology (ESC) guidelines(1) as an electrocardiogram (ECG) rhythm showing at least 30-second absolutely irregular R-complex to R-complex intervals without discernible P-waves.

AF usually starts as intermittent, infrequent short episodes and then progresses to more frequent episodes of long duration(1–5), finally becoming persistent AF. AF is accordingly classified as:

1 – Paroxysmal AF: An AF episode that terminates within seven days spontaneously or with cardioversion.

2 – Persistent AF: When the AF episode lasts longer than seven days but terminates within one year spontaneously or with cardioversion.

3 – Long-standing AF: When AF continues for more than one year but the aim is still to restore sinus rhythm.

4 – Permanent AF: When persistent AF rhythm is accepted by both the patient and the physician.

5 – First-diagnosed AF: When AF is diagnosed for the first time irrespective of its duration.
Based on the presentation (1), AF is also classified as:

1 – Asymptomatic AF: When the AF episode is not associated with AF symptoms. Many patients have asymptomatic AF.

2 – Symptomatic AF: When the AF episode presents with palpitation, dyspnoea, chest tightness, fatigue, weakness, dizziness or syncope. The severity of symptoms varies from mild to a disability that affects normal daily activities.

1.2 PATHOGENESIS

Several trigger factors interact with multiple precipitating factors for the development of AF (Figure 1). Atrial ectopic(6) focus enhanced by increased sympathetic activity(7) and toxic and inflammatory mediators(8) may trigger atrial tachycardia. Structural cardiac changes such as atrial remodelling, fibrosis(9), necrosis(10) and myocyte hypertrophy may dissociate the electrical conduction system(10, 11) between muscle bundles and local conduction, resulting in re-entry atrial arrhythmia. Genetic predisposition to developing AF and its progress has been recently shown in a meta-analysis study(12).

Pathogenesis and Risk factors for AF

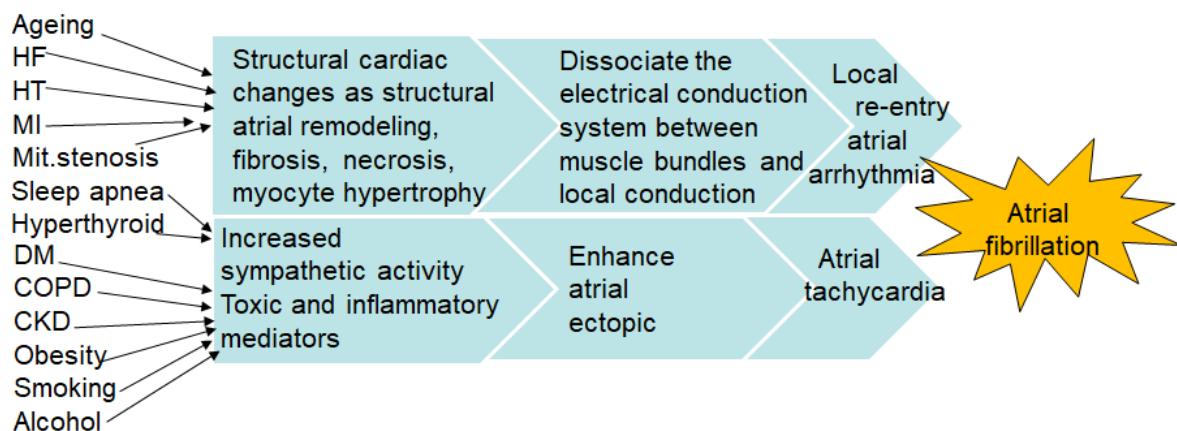


Figure 1. Pathogenesis and risk factors for AF

HF, Heart failure; HT, Hypertension; MI, Myocardial infarction; Mit, Mitral; DM, Diabetes mellitus; COPD, Chronic obstructive pulmonary disease; CKD, Chronic kidney disease.

1.3 RISK FACTORS FOR ATRIAL FIBRILLATION AND PREVALENCE

Aging is the strongest risk factor for the development of AF(13–15). The prevalence of AF increases with age(16, 17), particularly over 65 years of age. Male gender is another risk factor associated with incident AF(15, 18).

Cardiovascular diseases(16, 17, 19) such as hypertension (HT), congestive heart failure (CHF)(14), myocardial infarction(14) and mitral stenosis(20) are strong risk factors for AF. Non-cardiovascular diseases as risk factors for AF include diabetes mellitus (DM)(16), hyperthyroidism(21), sleep apnoea(22, 23), chronic obstructive pulmonary disease (COPD)(24) and chronic kidney disease(25).

Lifestyle factors such as smoking(26), alcohol consumption(27), vigorous exercise(28) and obesity(16, 29–31) are other risk factors for AF. CHARGE-AF(13) is a validated model for predicting the risk of incident AF.

AF is a common arrhythmia that affects around 3–3.5% of adults aged 20 years and older(32). AF prevalence increases to 4.4% among individuals 65 years and older(33) and to 12% among 75–76-year olds(34). The prevalence of AF has increased as a result of population ageing(19). The prevalence of AF is expected to continue to increase significantly in the coming decades(35).

1.4 IMPACT OF ATRIAL FIBRILLATION

Around 2/3 of the AF population has symptomatic AF that affects the quality of normal daily life activities(36). This may require hospitalization, cardioversion, antiarrhythmic treatment or AF ablation. In contrast, around 1/3 of the AF population appears to be asymptomatic (37), thus running a higher risk of not being detected. A study(38) reported a 67.1% health self-assessment score among patients with controlled AF compared to 63.2% among patients with uncontrolled AF.

Stroke

The greatest problems associated with AF are the complications of AF, primarily thromboembolic stroke. Asymptomatic AF patients have as high a risk of thromboembolism as symptomatic AF patients(39). Around 30% of ischemic strokes are related to AF(40). AF increases the risk of stroke by around five times(41). The stroke risk of AF is validated by scores such as CHA2SDS2-VASc(42) and ABC(43). Mortality and chronic severe disabilities are high in strokes related to AF(44). Patients with strokes require a high level of care, including primary health care (PHC), hospital care(45), rehabilitation and social care. Consequently, strokes also increase the social burden on the community(45). However, oral anticoagulants (OAC) are highly effective in preventing ischemic strokes associated with AF(46). Thus, early detection of AF and treatment of high-risk patients with OAC may prevent a high number of strokes.

CHF

CHF is a risk factor for AF(16, 47). However, AF itself is a predictor of the development and progress of CHF(48). The development and progress of CHF may be delayed by the early detection and management of AF. Tachycardia-induced cardiomyopathy(49) associated with AF can be a consequence. Such cardiomyopathy is reversible if it is corrected at an early stage. Mortality increases by increasing the heart rate over 100 beats/minute in patients with CHF and AF(50). Thus, rate control therapy is recommended(1) in AF with high heart rate.

Dementia

There is strong evidence to suggest that AF is significantly associated with the development of dementia(51–53). Dementia is a disabling disease that places a high burden on the community. Large register-based studies have suggested that the use of OAC in AF patients is associated with a lower prevalence of dementia(54, 55).

1.5 DIAGNOSTIC METHODS FOR ATRIAL FIBRILLATION

1.5.1 ECG TECHNIQUES

Single time-point ECG

Diagnosis of AF requires a documented 30-second ECG showing completely irregular R-R intervals without distinct P-waves(1). Non-paroxysmal AF is easy to detect using single-time-point ECG recorders. However, paroxysmal AF is not easy to detect using single time-point ECG when AF episodes are infrequent and of short duration. Thus, continuous ECG monitoring (56) or intermittent ECG(57) recording over a long duration are recommended for detecting such paroxysmal AF. There are many types of ECG monitoring devices for detecting AF (Figure 2).

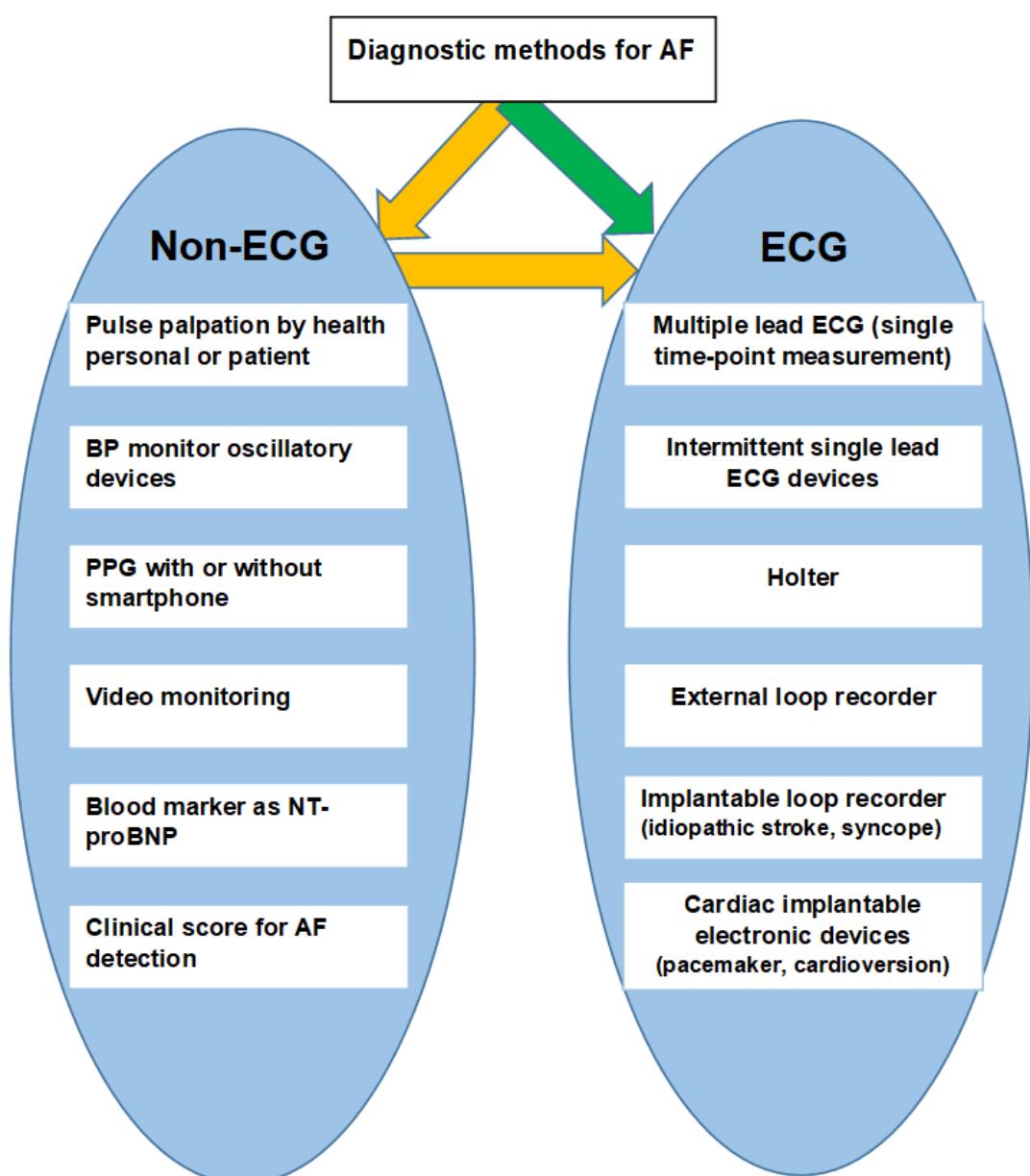


Figure 2. Diagnostic methods for AF

BP: blood pressure, PPG: photoplethysmography

Prolonged ECG monitoring

Traditional 24-hour Holter monitoring has a low sensitivity to detecting paroxysmal AF(58). ECG monitoring over seven days increases AF detection compared to monitoring for less than 48 hours(59). A single-lead portable ECG could be easier to use for AF screening compared to traditional Holter monitoring. A meta-analysis(60) showed a comparable AF detection rate using repeated single-lead ECG recordings compared to 24-hour Holter monitoring. However, this study showed potential heterogeneity in the AF detection rate depending on monitoring time. Thus, 5–14 day ECG recordings (34, 61) are preferable for detecting AF, particularly in high-risk groups such as patients with stroke. Intermittent short ECG recordings such as Zenicor(62), Mydiagnostick(63) and AliveCor(64) have been validated for the detection of AF and are a sensitive, easy and accepted technique for AF screening.

Other ECG recordings: In recent years, many types of adhesive patch ECG (65) monitors for 5–14 days have been available on the market. The advantage of this kind of ECG is that it is easy to use over a long duration and is accepted by the screened persons. Prolonged monitoring over many months using an implantable subcutaneous ECG monitor(66) has recently been used for the detection of paroxysmal AF in high-risk patients such as patients with cryptogenic stroke.

1.5.2 NON-ECG TECHNIQUES

Many supporting non-ECG techniques (Figure 2) are used for AF detection. These techniques include pulse palpation(67), oscillometric blood pressure measurement (or a combination of pulse and BP)(68) and the use of blood markers for AF such as N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) level(69, 70). Recently, other new techniques have been validated for AF detection such as contact-free facial photoplethysmographic video recordings(71). Plethysmography recordings with smartphones(72) or smartwatches(21) have been used to detect patients suspected of having AF. These simple and easy techniques could be used as a cost-effective way of assisting AF screening. A recent study has shown a very high accuracy of algorithms for smartphone applications in detecting AF using plethysmography(73). However, difficulties were encountered in interpreting many of these recordings(74, 75). Moreover, such techniques should be complemented by an ECG test for at least 30 seconds in order to verify the presence of AF.

Single time-point pulse palpation is often recommended for AF detection but the role of cardiac auscultation in AF detection has not been validated, although cardiac auscultation such as pulse palpation is part of routine clinical examinations.

Pulse palpation for AF screening

According to the ESC guidelines for AF 2016(1), it is recommended (Class I) to screen all patients aged 65 years and older using pulse palpation to detect AF. This recommendation is based on a randomized control study(76) showing that screening using pulse palpation detects a comparable proportion of AF compared to screening using single time-point ECG. It is therefore a cost-effective set for AF screening.

A systematic review(67) of multiple studies shows the validity of pulse palpation in AF screening. In some of these studies, healthcare professionals (76) such as physicians and nurses took the patient's pulse while, in one trial, the patients themselves checked their own pulses(77). Pulse palpation by a nurse(76) showed 87% (95% CI 82% to 91%) sensitivity and 81% (95% CI 80% to 83%) specificity for AF detection. Participants in one pilot study for self-pulse palpation were highly motivated to continue checking their own pulses over many weeks(78).

AF detection by automated oscillatory BP monitoring devices

A four-month trial(79) to detect AF in a primary care setting using an oscillatory BP device as a single-time-point measurement compared to an ECG was feasible and showed 80.6% sensitivity and 98.7% specificity. A recent meta-analysis(80) showed 91% sensitivity and 96% specificity for AF detection using BP devices with an algorithm for AF detection. Another meta-analysis(81) for AF detection showed increased accuracy with 99% sensitivity by taking three sequential readings on the same occasion where at least two readings showed AF. As AF screening on a single time-point occasion has limitations in detecting paroxysmal AF, repeated measurements could detect more AF, including paroxysmal AF. 24-hour ambulatory BP monitoring compared to simultaneous ECG monitoring could detect 93% of AF paroxysms that were detected using ECG(82). Furthermore, daily BP monitoring at home for 30 days showed a 99.2% sensitivity and 92.9% specificity for AF detection, compared to a simultaneous ECG recording(83).

The role of NT-proBNP in the detection of AF

NT-proBNP is a peptide secreted from the cardiac muscle, mainly from the atrial muscle as a result of cardiac muscle stretching(84). NT-proBNP can be used as a biomarker for AF prediction (13, 31, 85–87). Moreover, NT-proBNP can predict strokes(43, 88) and mortality in patients with AF. Thus, using NT-proBNP in AF screening may increase the utility of the screening. Furthermore, screening-detected AF cases with a high NT-proBNP carry a higher risk of stroke than those cases with a relatively lower NT-proBNP.

1.6 SCREENING STRATEGIES FOR ATRIAL FIBRILLATION

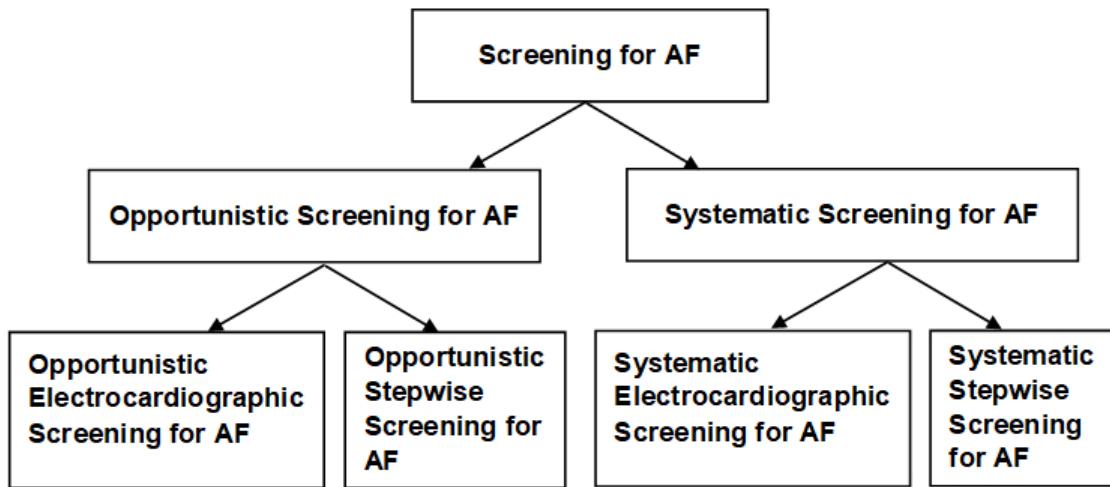


Figure 3. Classification and techniques used in AF detection

AF screening can be classified in various ways, such as screening settings, screening technique, screening driver and target population. It may be preferable to primarily classify AF screening as systematic or opportunistic (Figure 3). Each of these types of classification could be further subclassified into electrocardiographic screening and stepwise screening, resulting in four screening strategies.

Opportunistic electrocardiographic screening(89–91)

Opportunistic stepwise screening(92–94)

Systematic electrocardiographic screening(56, 95–97)

Systematic stepwise screening(70, 98, 99)

The primary classification depends on how the target population is invited (such as specific age) to the AF screening. In systematic screening, the target population is invited via post, e-mail or social media, while opportunistic screening is used when there is a special opportunity to do so, for example, when patients visit a primary healthcare centre (PHCC), pharmacy or are being vaccinated. Thus, opportunistic screening is expected to catch more patients with a high morbidity than systematic screening. Such patients may even be more motivated to participate in the screening(100), particularly if they are invited by their physician when seeking care.

Some authors(101) classify AF screening as a third type of so-called target screening, including screening patients with a high-risk disease such as stroke(56), CHF and sleep apnoea. Screening patients at high risk of AF increases the yield of the screening programme. However, this type of classification is uncommon and it may be preferable to consider this type of screening as systematic screening in which, for example, all patients with stroke should be invited to the screening according to the guidelines(1).

Basically, ECG recording is mandatory for diagnosing AF. However, an ECG examination is both time consuming and resource consuming, particularly when using intermittent or prolonged ECG monitoring. Thus, stepwise screening could be a resource-saving alternative. Stepwise screening comprises two stages: The first stage is screening using non-ECG techniques to detect those cases that are highly suspected of having AF. The second stage is screening using an ECG recorder for those cases suspected in the first stage. Thus, the technique used in the first stage of stepwise screening should be highly sensitive and less time consuming and resource consuming than the ECG stage for considering such types of screening.

A recent mass AF screening study(102) using a seven-day photoplethysmography smartphone application showed 1.1% possible AF rhythm but was not verified by ECG.

There have been few randomized controlled studies for AF screening. One study compared opportunistic stepwise screening using pulse palpation with systematic stepwise screening(103). In the SAFE(76, 104) study, opportunistic stepwise screening using pulse palpation was compared to systematic electrocardiographic screening. In addition, combined interventional screenings compared with AF detection by routine care.

As well as the AF screening classification described above, depending on screening settings and screening techniques, AF screening could be also classified depending on screening driver into PHC-driven and community based. Compared to community-based AF screening(34, 98), PHC-driven AF screening(93, 100) showed a higher participation rate and probably screened patients with a higher comorbidity associated with AF. The initiation rate of OAC in preventing stroke in detected AF patients is high in PHC-driven AF screening(93).

Although the detection of AF depends on a risk factor for AF, it also depends on the screening strategy. A meta-analysis(33) for single time-point AF screening showed an overall detection rate of 1.0%, which increased to 1.4% among individuals aged 65 years and older.

A recent meta-analysis(105) showed that systematic AF screening was more effective than opportunistic AF screening (1.8% vs. 1.1%), PHC-driven AF screening than community-based screening (1.9% vs. 1.1%) and AF screening by repeated heart rhythm measurements than screening by isolated assessments of rhythm (2.1% vs. 1.2%).

1.7 DETECTION OF CONCOMITANT CARDIOVASCULAR DISEASES

Many morbidities (16) such as HT, DM, ischemic heart disease and CHF predict AF incidence. Some of these AF predictors such as HT and DM are also risk factors for stroke, regardless of AF(42, 106–108). Thus, AF screening combined with early detection and management of comorbidities such as HT(90, 109) and DM(110) may prevent strokes, in addition to the use of OAC for AF cases. An integrated care approach is defined as a coordinated system of care that includes multidisciplinary teams to manage patients with

chronic diseases and to ensure they are actively involved in their management. A meta-analysis(111) showed that integrated care for patients with AF reduces mortality and cardiovascular hospitalization compared to usual care. Thus, integrated screening and management of AF (and its comorbidities) may be essential.

1.8 COST-EFFECTIVENESS OF SCREENING

Given scarce resources, the goal of most healthcare systems is to provide as much health care as possible. Thus, any screening programme should be cost-effective even if other parameters such as ethical perspectives must be considered. Many studies have evaluated the cost-effectiveness of AF screening (112–119). AF is known as a risk factor for stroke(41), which places a high burden on the community(2, 16), including high mortality and chronic disabilities.

Although long-term treatment with OACs can be costly, they are effective(120) in preventing stroke in AF patients with a high risk of stroke. The protective effect of OAC outweighs the risk of bleeding (121).

The cost and outcome of AF screening varies according to the screening method and the target population. Screening using single time-point ECG measurement or pulse palpation is easy and inexpensive. However, it is hard to detect paroxysmal AF using such a screening method. While continuous ECG monitoring(40) or intermittent ECG recording(43) over a long duration are sensitive methods for detecting all types of AF, such screening methods are more costly and time consuming. However, one study showed that it is more cost-effective to screen using intermittent ECG than with single time-point ECG screening(113).

Screening individuals at a high risk of AF detected a relatively high proportion of AF cases(122). A systematic review(101) of systematic single time-point screening studies showed that the total AF prevalence was 14% among patients 75 years and older versus 5.1% among 65–74-year olds, in which around one third of AF cases were undiagnosed. Thus, screening of elderly persons over 75 years of age yields more AF cases than screening a younger age group such as 65–74-year olds(123). However, detecting AF cases in a younger age group may be more beneficial in preventing a high number of strokes in a relatively young age group compared to screening elderly persons over 75 years of age. Further, elderly persons generally visit healthcare centres more frequently and the proportion of undetected cases could therefore be theoretically lower in such a population.

1.9 TO SCREEN OR NOT TO SCREEN?

The ESC(1) recommends AF screening for a specific target population. The WHO's screening criteria are applicable to AF screening (Table 1). However, there are a number of arguments against generalizing mass population screening for AF(124–126). There is

growing evidence to suggest that the risk of thromboembolic stroke could be related to atrial cardiomyopathy rather than to AF. In contrast, a recent study(127) showed that AF adjusted to left atrial enlargement is an independent risk of stroke whereas there was no association between stroke and left atrial enlargement.

Table 1. Validity of a screening programme according to WHO criteria developed by Wilson and Jungner(128)

Criteria for a valid screening programme according to the World Health Organization	Applicability of AF screening
<ul style="list-style-type: none"> • The condition sought should be an important health problem. • There should be a recognizable latent or early symptomatic stage. • The natural history of the condition, including development from latent to declared disease, should be adequately understood. 	<p>AF is a risk factor for stroke(41) with high mortality(129) and disabilities. AF is also a risk factor for dementia(52, 53).</p> <p>AF early stage as an infrequent paroxysm usually progresses(2–4) to a high AF burden that is associated with more strokes. Even early asymptomatic AF is associated with a high stroke risk(39). Asymptomatic AF can be detected using ECG monitoring(56) or intermittent ECG(34).</p>
<ul style="list-style-type: none"> • There should be a suitable test or examination. • The test should be acceptable to the population. 	<p>Non-invasive ECG monitoring(56, 65) and intermittent ECG (34, 57, 61–64) are sensitive tests for detecting AF and cause no harm. Using such intermittent ECG techniques is easy and accepted (64).</p>
<ul style="list-style-type: none"> • There should be an accepted treatment for patients with a recognized disease. • There should be an agreed policy on whom to treat as patients. 	<p>OAC is an effective therapy(120) for preventing stroke in AF patients with a high risk of stroke stratified by a CHA2DS2-VASc score(1). It has been suggested that AF patient treated with OAC appear to have less dementia(55).</p>
<ul style="list-style-type: none"> • Facilities for diagnosis and treatment should be available. • The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. • Case finding should be a continuing process and not a “once-and-for-all” project. 	<p>Several studies have reported that AF screening is feasible(34, 89, 91, 130). Screening facilities are available that use various ECG techniques(101), interested health personnel(131), as well as feasibility of initiating AC therapy(130).</p> <p>Many studies(112, 114, 116, 117, 119, 132, 133) based on simulation analysis have reported that AF screening is cost-effective.</p> <p>A simulation analysis(114) has reported the benefit of repeated AF screening at one–five year intervals.</p>

There is a controversy regarding whether screen-detected AF cases have the same risk for ischemic stroke and mortality rate as AF cases detected by usual care(125, 134). Although asymptomatic AF cases(39) and incidental AF cases detected by usual care have a high stroke risk, it is unclear whether cases of low AF burden detected by screening have an increased stroke risk (Figure 4). The benefit of AC therapy in preventing ischemic stroke in AF cases detected by usual care outweighs the increased risk of bleeding(120). However, the threshold of AF burden among screen-detected AF cases that justify AC therapy is unknown.

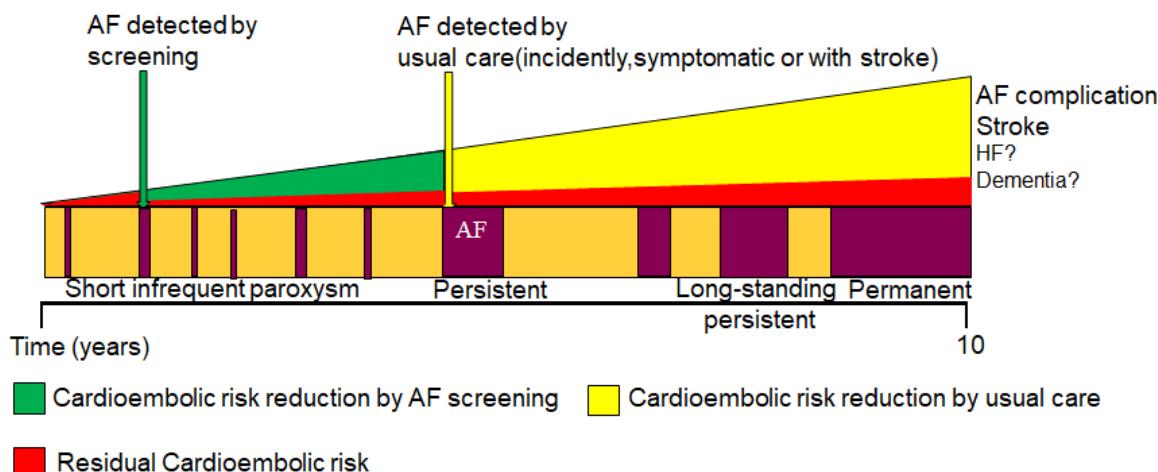


Figure 4. Progress of atrial fibrillation and its detection

Although the accuracy of ECG techniques in detecting AF is high(101), there is a small proportion of false-positive cases that require supplementary diagnostic tests and probably unnecessary AC therapy. This low false-positive rate is probably acceptable for investigating symptomatic patients seeking usual care. However, it has not been investigated whether such a false-positive rate is accepted by the screened individuals. The screening process may cause some anxiety among the screened population. The potential harm of AF screening should be further evaluated.

Thus, randomized trials are needed to evaluate the stroke and mortality outcomes of AF screening. If such trials show the clinical benefit of AF screening, the cost-effectiveness based on these screening trials should be evaluated. The benefit of repeated AF screening could then be subsequently assessed.

2 AIMS

The overall aim of this thesis was to study the feasibility of a screening programme for AF using intermittent electrocardiography in a primary healthcare setting and the initiation of anticoagulants to prevent stroke among detected cases of AF.

The specific aims of the thesis were:

1. To assess the participation rate in AF screening and possible factors that affect participation.
2. To investigate the prevalence and detection rate for AF using intermittent ECG and predictors of AF detection at various ages.
3. To evaluate the initiation rate of OAC in patients with newly detected AF cases in primary care.
4. To evaluate the safety of AF screening in PHC.
5. To assess the cost-effectiveness of AF screening in PHC.
6. To evaluate the role of NT-proBNP level in AF screening.
7. To validate the value of self-pulse palpation in detecting AF compared to “simultaneous” ECG registration.

3 METHODS

3.1 SETTING AND STUDY POPULATION

This thesis is based on two cross-sectional screening studies (studies I and IV) for AF (Figures 5 and 6). The target population in the first study comprised 70–74-year-old individuals registered at Högdalen PHCC during the 2015 screening period while in the second study, the target population were patients 65 years of age and older without known AF who attended four different PHCCs during a screening period from June 2017 to December 2018. Thus, the latter screening is considered to be opportunistic screening while the first screening was regarded as systematic. However, the majority of the participants at the first screening were recruited when they visited the PHC. The responsible researcher was working as a general practitioner at Högdalen PHCC at the time of the screening. We therefore decided to screen at the same care centre. In the second screening study, we decided not to screen in Stockholm County as another screening study for AF was taking place at the time. We therefore selected four PHCCs around Stockholm County.

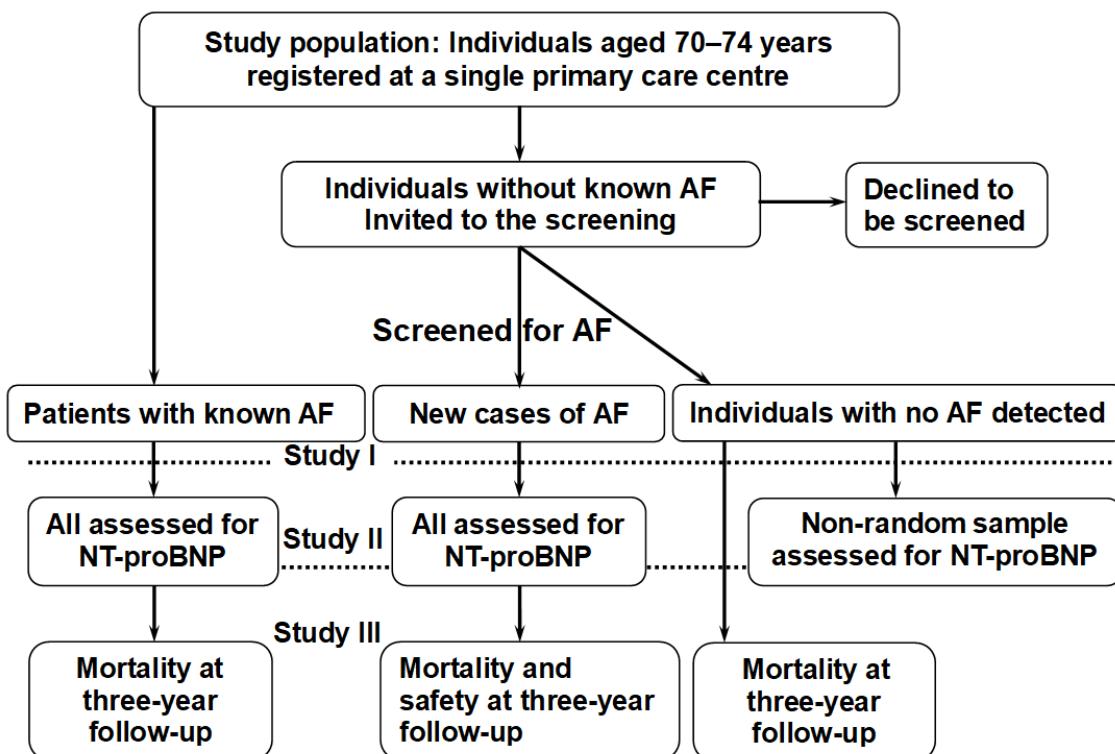


Figure 5. Flow diagram illustrating the design of studies I–III

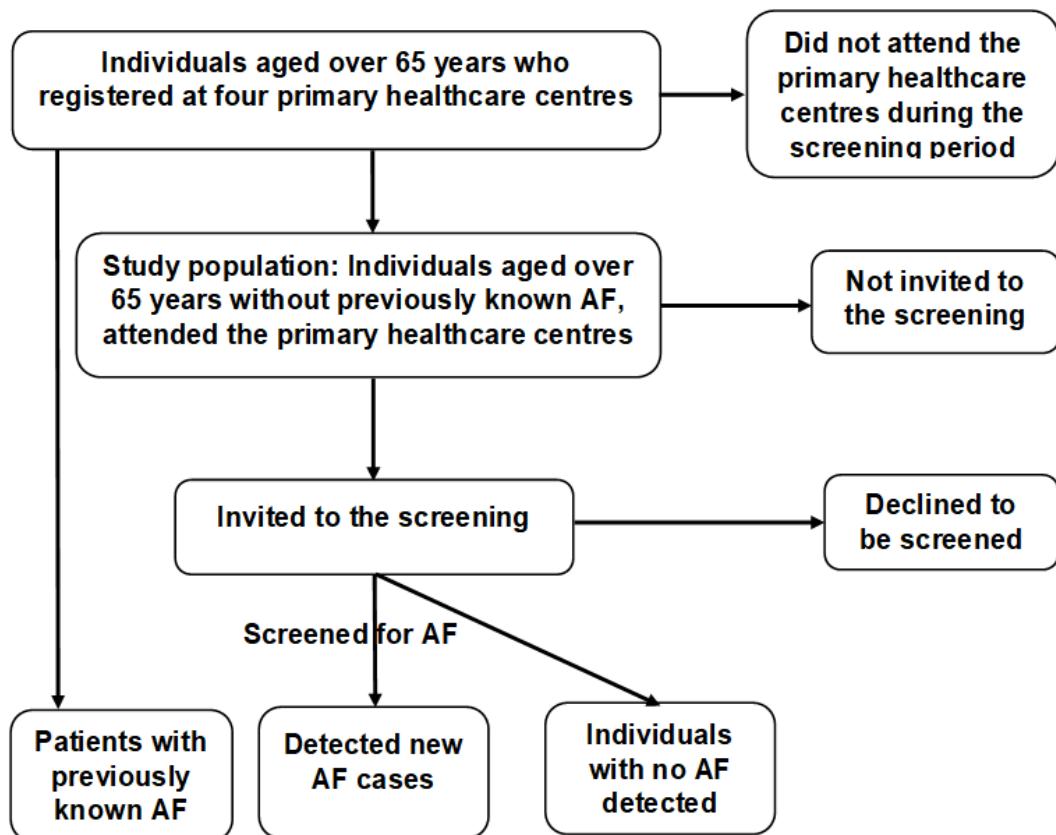


Figure 6. Flow diagram illustrating the design of study IV

In study II, plasma NT-proBNP levels were evaluated in participants from the first screening study. NT-proBNP was analysed for all new cases of AF and all known cases of AF. Of those individuals with no detected AF, a non-randomly selected group of 53 individuals (18%) was also checked for NT-proBNP.

Study III was a cohort study of the safety of AF screening in which all participants from the first screening study were followed up for three years for mortality. In addition, adherence to AC therapy among new AF cases and the occurrence of severe bleeding and stroke were evaluated at a three-year follow-up. In this study, we also assessed the cost-effectiveness of the first screening study using a Markov model simulation analysis based on our screening results combined with some assumptions obtained from previous studies.

In study IV, we also evaluated the validity of self-pulse palpation for the detection of AF.

3.2 SCREENING PROCEDURE

In study I, patients with previously known AF were invited to routine visits at the PHCC for follow-up according to national recommendations. AC therapy was recommended for patients with known AF unless there was a clear contraindication. Individuals with no previously known AF were invited to participate in the screening programme. The remaining

individuals who did not visit the PHCC during the first 10 months of the inclusion period received two written invitations to participate.

Participants with no previously known AF were examined using a 12-lead ECG. If the ECG showed no AF, intermittent ECG recordings were conducted for 30 seconds three times a day, and if palpitations occurred. Intermittent ECG monitoring was performed for at least two weeks. An extended recording period was implemented in cases of infrequent recordings and suspected arrhythmia.

A Zenicor handheld ECG with an integrated mobile transmitter was used. When handheld ECG findings indicated AF or any other suspected pathological findings, the ECG was re-examined by an experienced cardiologist to confirm the diagnosis. Individuals with unclear or uninterpretable ECGs were further investigated using Holter monitoring. AC treatment was offered to patients with newly detected AF.

The screening procedure used in study IV was the same as the screening procedure used in study I but with the following differences:

1. Patients with previously known AF were not evaluated in study IV.
2. Only those patients who attended the PHCCs were invited to participate in this study. Thus, there were no written invitations.
3. One to two nurses were assigned per centre in this study to recruit patients for the screening while the responsible researcher conducted the screening in the first study. The nurses had received prior training in AF and pulse palpation.
4. The nurse carefully instructed participants in the technique of radial pulse palpation to be performed at home three times per day over a two-week period simultaneously with intermittent ECG recordings using a Zenicor handheld ECG.
5. No 12-lead ECG was used.
6. Individuals with unclear handheld ECG recordings were further investigated using an external loop recorder while Holter monitoring was used in the first screening study.

3.3 DATA COLLECTION

In study I, the participants completed a health questionnaire. The responsible physician at the PHCC also reviewed the participants' medical records, including their current medications, and performed a general medical examination that included body weight, height, pulse, blood pressure and fasting plasma glucose measurements.

In screening study IV, the participants completed a health questionnaire about comorbidity according to the CHA2DS2-VASs score during a 30-minute consultation with a nurse who also measured their body weight, height, pulse and blood pressure.

In study II, the results of the NT-proBNP of the participants in study I were retrieved from the patients' medical records.

In study III, the follow-up results about mortality, AC adherence, occurrence of stroke and severe bleeding were retrieved from the patients' medical records. In the cost-effectiveness analysis, cost and resource use data were primarily obtained from the healthcare regions of Sweden and the published literature.

AF was defined based on the ESC guidelines(1) as a 30-second recording with completely irregular R-R intervals without distinct p-waves.

The CHA2DS2-VASc(42) score was used to assess the risk of systemic thromboembolism.

CHF was defined according to the ESC guidelines(1) as typical symptoms (e.g. breathlessness and ankle swelling) caused by structural and/or functional cardiac abnormalities. Echocardiography and plasma NT-proBNP tests were used for diagnosing unclear cases.

HT was diagnosed as brachial artery systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two different occasions. Digital blood pressure measurements were used at rest in a sitting position.

For diagnosis of DM, fasting plasma glucose >7.0 mmol/L was used on two different occasions in accordance with the recommendations of the World Health Organization.

To quantitatively measure the participants' self-health assessment, an EQ visual analogue scale developed by the EuroQol Group was used.

The European Heart Rhythm Association score was used to evaluate physical capacity, but we mistakenly reported in published papers that we had used the New York Heart Association's functional classification.

Body Mass Index (BMI) was calculated by dividing the body weight (mass) in kilograms by the square of the height in metres.

3.4 STATISTICAL METHODS

Categorical data were summarized by counts and percentages. For all continuous variables, visual inspection of histograms and the Shapiro-Wilk's test were used to assess the deviation from a normal distribution. Normally distributed continuous data are reported as means with standard deviations, whereas non-normally distributed data are reported as medians with

interquartile range(IQR). Fisher's exact test was used to analyse categorical variables. For comparison of the means and the medians of continuous variables between two groups, the Student's t-test and the Mann-Whitney U-test were used, respectively. For comparisons of the means and the medians of the continuous variables between three groups, an analysis of variance and Kruskal-Wallis tests were used, respectively. Odds ratios (ORs) with 95% CIs were used to test for associations between AF and risk factors. Univariate logistic regression analysis was used in study I, while multivariate logistic regression analysis was used in studies II and IV. In all four studies, a probability value of 0.05 was considered statistically significant for all tests. The analyses were performed using Stata statistical software version 10.

In study II, NT proBNP data were not normally distributed and were therefore normalized using natural logarithmic transformation, and the logarithmic mean was used in the regression test. Receiver operating characteristic analysis was performed and discriminative ability was assessed using the area under curve (AUC). Youden's index was calculated to determine whether it could be used to find a clinically relevant cut-off for NT-proBNP. The specificity balanced with the desired high sensitivity to different cut-offs was then studied to determine a clinically relevant cut-off value.

In study III, the mortality rate as outcome was treated as a time-dependent variable and calculated as incidence rates for the three cohort groups. Follow-up time was defined as years from inclusion in the AF screening to the date of death or was censored at the end of our observation. The cumulative incidence for the three cohorts was plotted using the Kaplan-Meier method and a log-rank test was used to compare the differences between cohorts with no AF as a reference group and the other two groups. Cox proportional hazards regression models were used to assess the mortality risk, HRs (HRs) and 95% CIs were calculated. A Markov model that simulated the disease progression was used to assess the cost-effectiveness of AF screening in study I but included the results of three-year follow-up data.

In study IV, sample size was calculated to show a statistically higher AF detection rate using an intermittent ECG over two weeks than an AF detection rate using a single time-point ECG on inclusion. We assumed a 1.4% AF detection rate using a single time-point ECG according to a previous meta-analysis for AF screening. We expected that total AF detection using a two-week intermittent ECG would be 3% depending on a previous study that used this screening method on 76-year-old patients. Using an alpha value of 0.05, a power 0.75 to calculate the sample size of the difference in the proportion between the two dependent groups yielded 955. Thus, we chose a sample size of at least 1,000. For pulse palpation in detecting AF, we constructed 2 x 2 contingency tables to enable calculation of sensitivity, specificity, positive predictive value and negative predictive value.

3.5 ETHICAL CONSIDERATIONS

The studies in this thesis were conducted in accordance with the principles of the Declaration of Helsinki. Studies I–III were approved by the Ethics Committee of Stockholm (DNR 2014/2061-31 and 2017/129-32) and study IV was approved by the Ethics Committee of Stockholm (DNR 2017/3:3).

All participants received verbal and written information about the study. The participants gave their written consent before entering the study and were informed that they were free to withdraw their participation at any time without this affecting their future health care. The collected data were handled in such a way as to ensure confidentiality.

In general, we could not recognize any negative consequences of participating in the studies, although we did not systematically check whether participation in our study caused any negative psychological effects.

In studies I and IV, screening was used to detect AF and to initiate AC to prevent stroke based on the assumption that screening-detected AF cases have as high a risk of stroke as AF cases detected by usual care. The benefit of ACs in preventing ischemic stroke should outweigh the risk of bleeding. A majority of detected AF cases received non vitamin-K ACs, which are safer than warfarin. At the three-year follow-up of the first screening study, we found no harm relating to AC treatment. There is no direct benefit for the participants in the studies in this thesis. However, it was assumed that those participants with detected AF benefited from AC.

No venous blood tests were taken in these studies. The results of NT-proBNP in study II were collected from patients' medical records.

4 RESULTS

4.1 PARTICIPATION

4.1.1 STUDY I

Of the 13,200 individuals who were registered at Högdalen PHCC in 2015, 415 (3.1%) were aged 70–74 years (Figure 7). This proportion was lower than the corresponding proportion (5.2%) of the Swedish general population in this age group. Females constituted 51.6% of the study population. This proportion was comparable to the corresponding proportion (51.2%) of females in the Swedish general population in this age group.

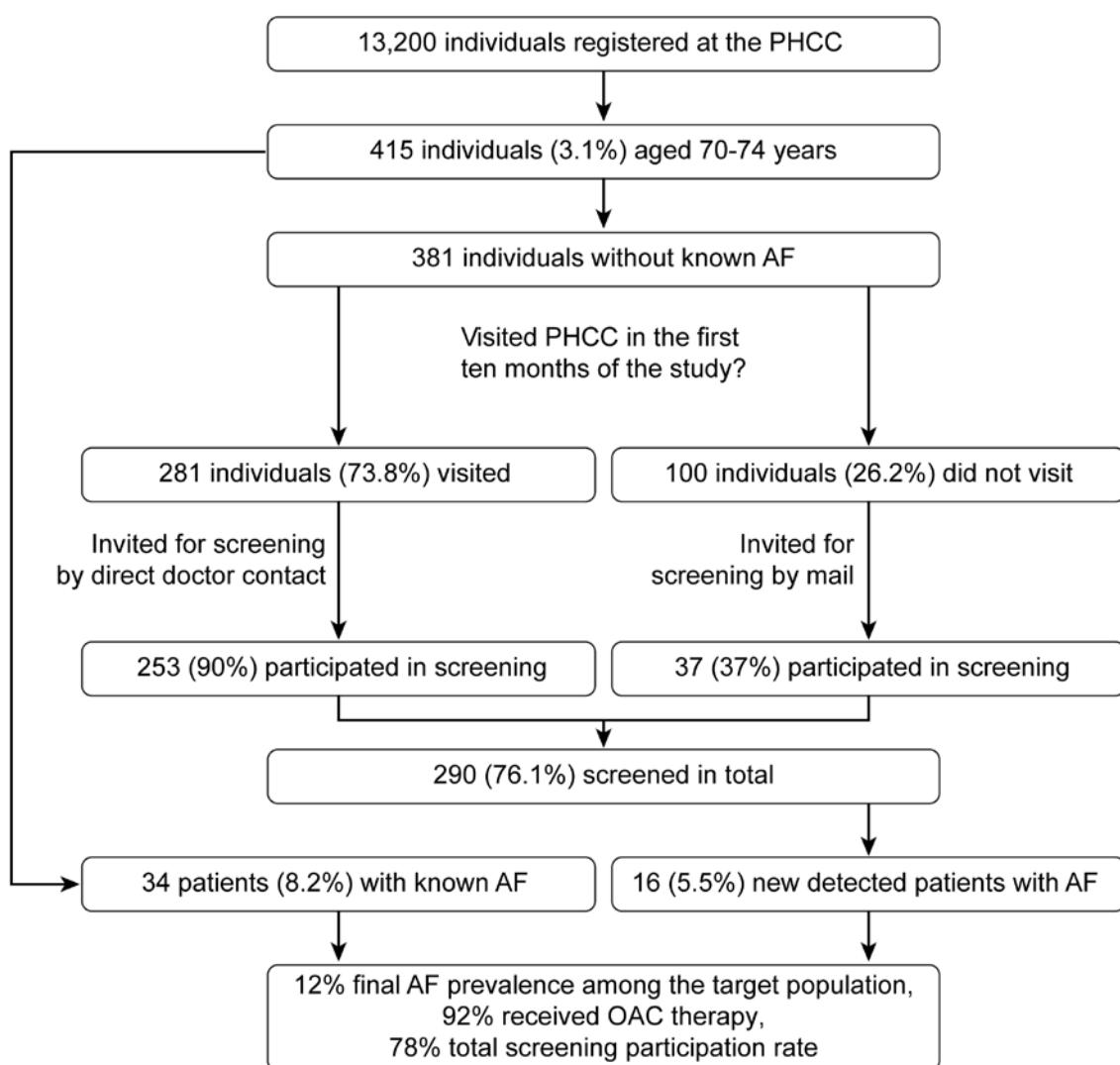


Figure 7. Flow diagram illustrating the screening results of study I. Reprinted courtesy of Ghazal F et al. (2018) Feasibility and outcomes of atrial fibrillation screening using intermittent electrocardiography in a primary healthcare setting: A cross-sectional study. PLoS ONE 13(5): e0198069.

Of the 415 registered individuals, 34 (8.2%) patients were already known to have AF (Figures 7 and 8). Of the 381 individuals with no previously known AF, 281 patients attended the research PHCC for various health consultations during the first 10 months of the screening period. These patients were invited to participate in the AF screening when they sought care and 253 patients (90%) participated in the screening, whereas 28 patients declined to participate. During the first ten months of the screening period, 100 individuals did not visit the PHCC and were invited by mail to the AF screening in the last two months of the study period. Of these 100 individuals, 37 participated in the screening, six individuals declined to participate and 57 individuals did not respond.

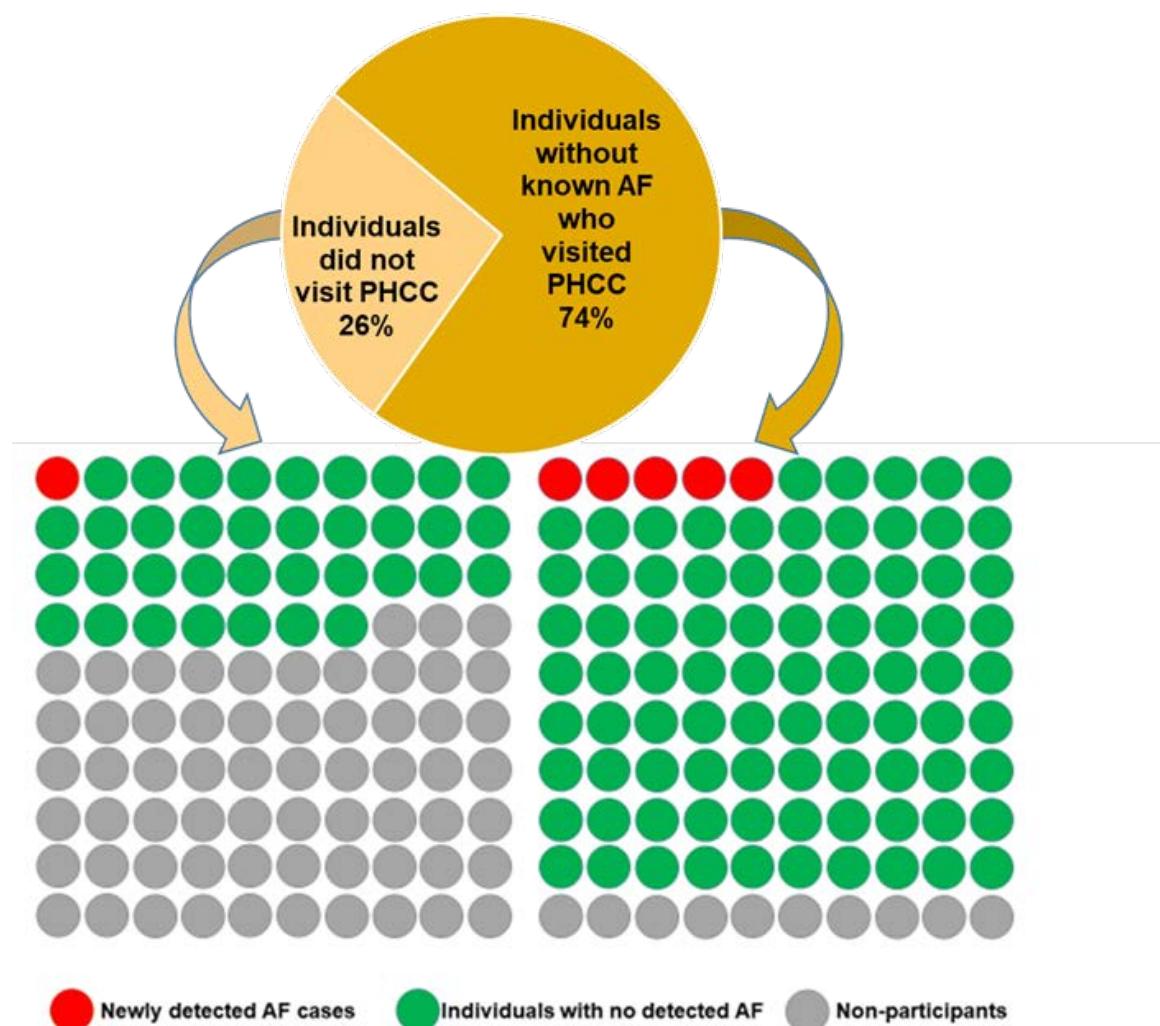


Figure 8. Chart illustrating the participation and AF detection rates using different modes of invitation in study I

The total participation rate in this study was 78.1% (95% CI, 73.8 to 82). The participants had significantly more cardiovascular disease than the non-participants (Table 2).

Table 2. Demographic characteristics and morbidity of the participants compared to the non-participants in study I. Reprinted courtesy of Ghazal F et al. (2018) Feasibility and outcomes of atrial fibrillation screening using intermittent electrocardiography in a primary healthcare setting: A cross-sectional study. PLoS ONE 13(5): e0198069.

	Participants 324 (78.1% of target population)	Non-participants 91 (21.9% of target population)	P-value
Diabetes mellitus N (%)	77 (23.8)†	7 (7.7)	0.000**
Hypertension N (%)	250 (77.2)†	27 (29.7)	0.000**
Congestive Heart failure N (%)	22 (6.8)	0 (0)	0.004**
Vascular diseases MI and/or PAD N (%)	41 (12.7)	5 (5.5)	0.035**
Previous Stroke, TIA, STE N (%)	30 (9.3)	4 (4.4)	0.096**
Female N (%)	169 (52.2)	42 (46.2)	0.186**
Age, year mean (SD)	71.9 (0.08)	72 (0.14)	0.564*

SD: Standard deviation, MI: Myocardial infarction, PAD: Peripheral artery disease

TIA: Transient ischemic attack, STE: Systemic thromboembolism

† Detected in medical records, blood pressure measurement and fasting blood glucose test

* Student's *t*-test

** Fisher's exact test

4.1.2 STUDY IV

Of the 46,477 individuals who were registered at four PHCCs in 2018, 9,224(19.85%) were 65 years of age and older. This proportion was similar to the corresponding proportion of the Swedish population (19.9%) but varied across the four centres. The recruitment of screening centres in the screening counties depended on the availability of nurses and their motivation.

Screening periods varied from 9 to 15 months in these centres in which screening initially started at two centres and then two more centres were recruited. However, the screening finished at all centres in December 2018 as a result of achieving the planned sample size. Screening was halted at all centres during the summer holiday. Furthermore, one of the first two centres stopped screening for three months because the nurse in charge was on sick leave.

Around 90% of registered individuals in the target population visited their PHCCs during the screening period. Of the visitors with no AF, 13% were screened (Figure 9), where only some

of these visitors were invited to be screened, depending on the capacity of health staff to screen. No real estimate of agreement to screening was made but the recruiting health personnel considered the agreement rate to be around 80–90%. The median age of the screened individuals was 72.1 years and 61.6% of them were female.

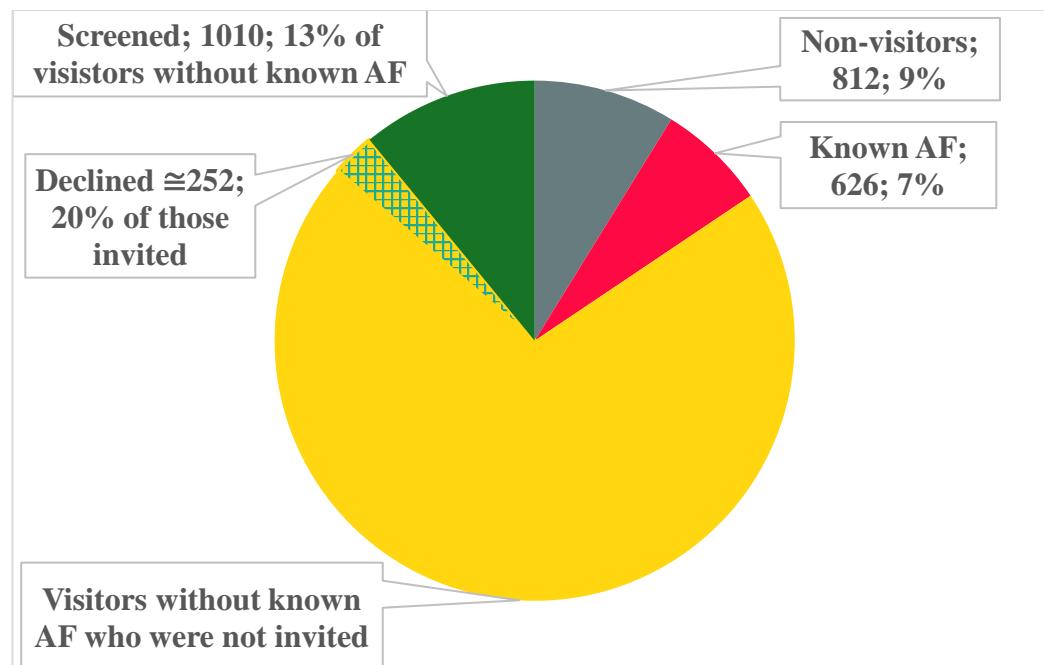


Figure 9. Distribution of the target population of study IV

4.2 ATRIAL FIBRILLATION DETECTION AND ITS PREDICTORS

4.2.1 STUDY I

A total of 290 individuals (76.1% of individuals without previously known AF) were screened using intermittent ECG. The median number of ECG recordings per individual was 39 (IQR 32, 46). Of these 290 individuals, 16 (5.5%) new cases of AF were detected (95% CI, 3.2 to 8.8). Three cases (1% of screened individuals) were detected using single ECG recording performed at the index visit at the PHCC. The remainder of the new AF cases were detected using intermittent ECG. Of the newly detected AF patients, ten patients had paroxysmal AF and six patients had non-paroxysmal AF. 12 patients (75% of the newly detected AF cases) had asymptomatic AF whereas four cases exhibited AF-associated palpitations. The pre-screening prevalence of AF was 8.2% and the prevalence increased through screening to 12% (95% CI, 9.1 to 15.6).

Predictors of AF cases

In an unadjusted model, detected AF cases had more prevalent sleep apnoea and higher DBP than those cases without AF (Table 3). In the groups evaluated for NT-proBNP and glomerular filtration rate (GFR), logarithmic mean NT-proBNP and DBP were independent

predictors of AF detection. The OR (95% CI) was 2.29 (1.11 to 4.69) and 1.08 (1.02 to 1.15), respectively.

In an unadjusted model, patients with known AF had more prevalent CHF and a history of previous stroke or transient ischemic attack than patients with newly detected AF. In the groups evaluated for NT-proBNP and GFR, only CHF was associated with known AF with an OR and 95% CI of 10.5 (1.24 to 89.92).

Table 3. Characteristics of participants without AF, patients with newly diagnosed AF and patients with known AF in study I

	Without AF 274 participants	New AF 16 patients	Known AF 34 patients	P-value
Age, mean year (SD)	71.9 (1.46)	72 (0.97)	72.6 (1.37)	0.019*
Female N (%)	148 (54)	7 (43.8)	14 (41.2)	0.299**
CHA2DS2-VASc Median (IQR)	3 (2,3)	3 (2,3)	4 (3,5)	0.001***†
Congestive heart failure N (%)	7 (2.6)	1 (6.3)	14 (41.2)	0.000** †
Hypertension N (%) post-screening	207(75.5)	13(81.3)	30 (88.2)	0.231**
Diabetes N (%) post-screening	59 (21.5)	6 (37.5)	12 (35.3)	0.078**
Stroke and/or TIA N (%)	21 (7.7)	0 (0)	9 (26.5)	0.003** †
MI and/or peripheral artery disease N (%)	30 (10.9)	3 (18.85)	8 (23.5)	0.075**
Chronic Obstructive Pulmonary Disease N(%)	26 (9.5)	2 (12.5)	9 (26.5)	0.017**
Sleep apnoea N (%)	5 (1.8)	3 (18.8)	2 (5.9)	0.004**
Health self-assessment score, median (IQR)	85(75,90)	88(68,90)	80(60,85)	0.003***
Body weight, mean kg (SD)	68.5 (13.5)	72.4 (19.1)	79.1 (9.5)	0.017*
Female				
Male	88.1 (15.7)	95 (13.2)	91.9 (14.8)	0.295*
BMI, median kg/m ² (IQR)	26.0(22.9,29.1)	23.5(22.6,31.7)	30.2(27.9,32.9)	0.010***
Female				
Male	28.1(25.9,30.4)	31.5(26.5,34.4)	28.3(26.6,31.6)	0.311***
BP, mean mmHg (SD)	146.3 (21.8)	146.4 (15.8)	134.7 (17.4)	0.011* †
Systolic				
Diastolic	82.4 (11.9)	88.9 (13.1)	85.9 (10.1)	0.033*

SD: Standard deviation, IQR: Interquartile range, TIA: Transient ischemic attack, BP: Blood pressure

*ANOVA (Bonferroni test for statistically significant differences among groups)

** Fisher's exact test

***Kruskal-Wallis test (Dunn test for statistically significant differences among groups)

All variables with the level of significance $p < 0.05$ are presented in bold

† Statistically significance differences between known AF group and new AF group, as well as differences between known AF group and group without AF

Detected DM, HT and other clinically significant arrhythmias

One case of clinically significant sinus bradycardia and one case of supraventricular tachycardia were identified. These cases were referred to a cardiac clinic for further evaluation.

Among all participants, 33 (10.2%) new cases of HT and eight (2.5%) new cases of DM were detected. Among the 217 patients with known HT, we detected 12 cases (5.5%) with very high blood pressure $\geq 180/110$ mmHg. Of these cases, seven had not been receiving antihypertensive treatment. HT was managed according to national recommendations.

4.2.2 STUDY IV

The pre-screening prevalence of known AF was 6.8% (95% CI 6.3 to 7.3%). A total of 1,010 individuals were screened and 27 (2.7%, 95% CI 1.8 to 3.9%) new cases of AF were detected. Only two new cases showed persistent AF while the other cases were paroxysmal. The two cases of persistent AF and three other cases of paroxysmal AF were detected by the first ECG recording on inclusion. Thus, the rate ratio for AF detection using intermittent ECG compared to single ECG measurement was 5.4 (95% CI 2.3 to 12.6). Of the 27 new AF cases, 16 (59%) were asymptomatic. 42 individuals had an unclear ECG and were further investigated using BioTelemetry ePatch continuous ECG monitoring for five days during which AF could be verified in four cases.

Predictors of detected AF cases

Table 4 shows the characteristics of newly detected AF cases with a median age of 76.4, predominantly male (70.4%) and more prevalent CHF. Age and male gender were independent predictors of detection of new AF cases with an OR (95% CI) of 1.14(1.07 to 1.21) and 4.46 (1.9–10.43), respectively. Figure 10 shows the age prediction for detection of AF.

Table 4. Characteristics of newly detected AF cases compared to those without AF. Reprinted courtesy of Ghazal F et al. (2020) Validity of daily self-pulse palpation for atrial fibrillation screening in patients 65 years and older: A cross-sectional study. PLoS Med.

	No atrial fibrillation 983 patients	Atrial fibrillation 27 patients	P-value
Age mean(SD)	72.7(5)	76.8(7)	<0.01
Age median(IQR)	72(69,76)	76.4(72,82)	<0.01
Female gender no. (%)	614(62.5)	8(29.6)	<0.01
Congestive heart failure no. (%)	13(1.3)	2(7.4)	0.01
Hypertension no. (%)	558(56.8)	15(55.6)	NS
Diabetes mellitus no. (%)	175(17.8)	3(11.1)	NS
Stroke/TIA no. (%)	77(7.8)	3(11.1)	NS
Myocardial infarction/peripheral artery disease no. (%)	74(7.5)	3(11.1)	NS
Systolic BP median(IQR)	140(129,152)	142(132,166)	0.1235
Diastolic BP median(IQR)	83(76,90)	83(77,92)	NS
BMI female median(IQR)	25(23,29)	28(25,31)	0.1939
BMI male median(IQR)	26(24,28)	25(24,29)	NS

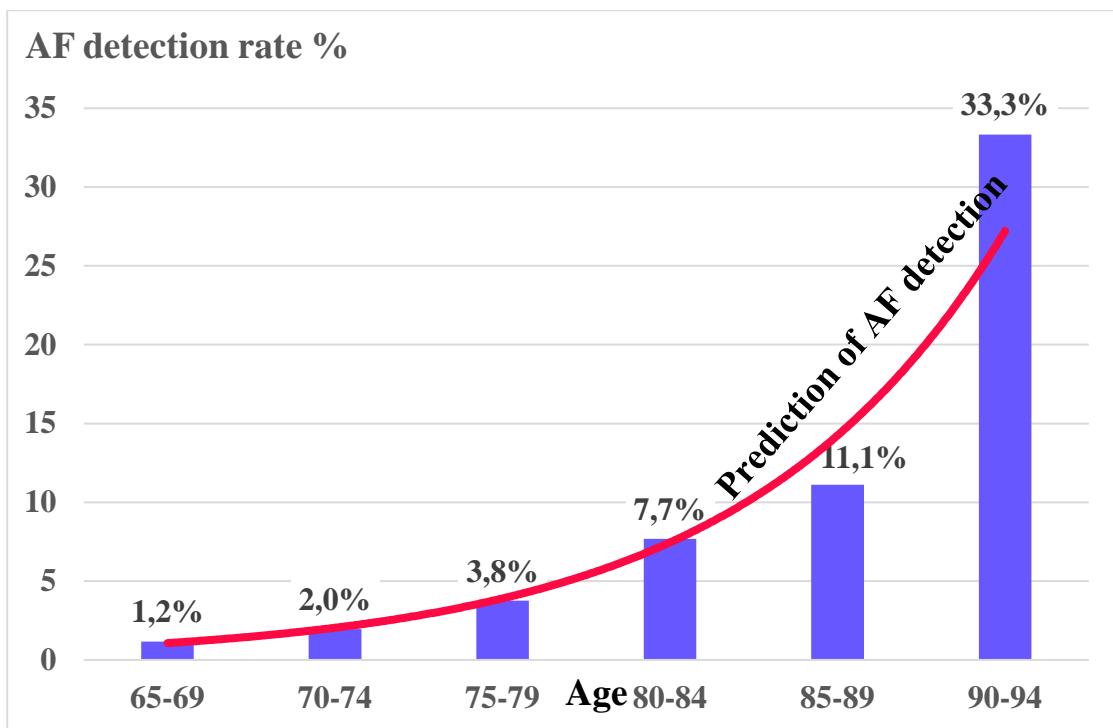


Figure 10. AF detection rate by age. Reprinted courtesy of Ghazal F et al. (2020) Validity of daily self-pulse palpation for atrial fibrillation screening in patients 65 years and older: A cross-sectional study. PLoS Med.

4.3 ANTICOAGULANT TREATMENT AND ADHERENCE

4.3.1 STUDY I

OAC therapy was initiated in 14 out of 16 (88%) newly detected AF cases. Six patients with previously known AF were not taking OAC, which we subsequently prescribed to four of these patients in our study. Thus, AC therapy was initiated in a total of 18 patients. Of all patients with AF, 92% received OAC therapy (95% CI, 80.8 to 97.8). Non-vitamin-K antagonist OAC were initiated in 15 (83%) patients and three (17%) patients were started on warfarin. Six participants without AF were already being treated with an AC for other indications. Among newly detected AF cases, OAC therapy was contraindicated in one patient whereas another patient refused the treatment.

ADHERENCE TO ANTICOAGULANT TREATMENT

Of the two cases who did not receive OAC in study I, one case had a contraindication for OAC due to concomitantly diagnosed bowel cancer. The other patient refused OAC treatment. At the three-year follow-up, one patient died, one had taken OAC 50% of the time and 13 patients had taken OAC regularly. Thus, overall OAC adherence was OAC 92%. Two patients were treated with vitamin K antagonists and the other patients were treated with non-vitamin K oral antagonists.

4.3.2 STUDY IV

AC treatment was initiated by the patient's general practitioner in 26 (96%, 95% CI 81–100%) of new AF cases. Non-vitamin K antagonist OAC were initiated in 25 patients and one other patient initially received OAC but then changed to low-molecular-weight heparins because of the side effects of bleeding. The physician in charge decided not to treat one patient with CHA₂DS₂-VASc, score one point (age 65–74).

4.4 SAFETY OF THE SCREENING

At the three-year follow-up in study III, overall OAC adherence was 92%. No stroke or severe bleeding was detected but one patient fell and suffered a muscle hematoma that disappeared spontaneously.

While the mortality rate among patients with known AF was higher than those with no AF (HR 3.6, 95% CI 1.5 to 8.7), there was no statistically significant difference in mortality rate between cases of new AF compared to cases of no AF (HR 0.86, 95% CI 0.12 to 6.44) (Table 5 and Figure 11). Patients with known AF had a higher mortality rate than those with new AF although the difference was statistically non-significant (HR 3.55, 95% CI 0.44 to 28.8).

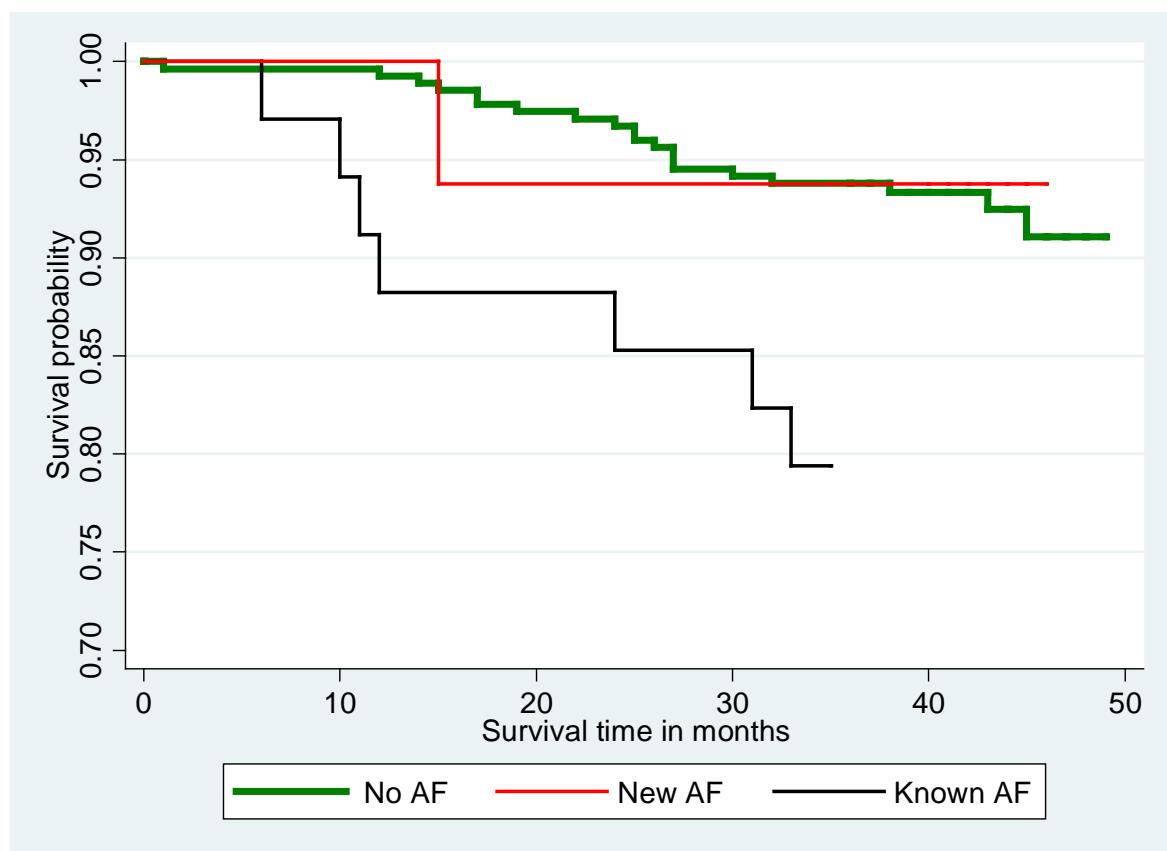


Figure 11. Kaplan-Meier survival curves: AF screening cohort stratified by AF groups

Table 5. Mortality rates and hazard ratios for AF groups

	Total persons	Total Observation Period (persons.year)	No. of deaths	Mortality rate (Death/100 persons.year)	Hazard ratio (CI)	*P-value
No AF	274	923	20	2.17	Reference	
New AF	16	53	1	1.89	0.86 (0.12–6.44)	0.887
Known AF	34	89	7	7.84	3.6 (1.5–8.7)	0.004

*The reference group is a cohort group with no detected AF

4.5 COST-EFFECTIVENESS OF THE SCREENING PROGRAMME

The cost-effectiveness of screening study I was evaluated at the three-year follow-up. Table 6 shows incremental cost, life years gained, Quality-Adjusted Life-Years (QALYs) gained and incremental costs per QALY for screening in primary care compared to no screening. The introduction of one-off screening in primary care generated 14 incremental QALYs and 15 incremental life years gained per 1,000 screened individuals. The incremental cost-effectiveness ratio (ICER) was EUR 2,389 per QALY gained.

Table 6. Base case cost-effectiveness results of AF screening in primary care

Treatment arms	Total costs (EUR)	Total life years	Total QALYs	Incremental cost (EUR)	Incremental life years	Incremental QALYs	ICER incremental (EUR/QALY)
No screening	2,346,586	11,229	7,744				
Screening	2,380,911	11,244	7,759	59,254	15.0	14.4	2,389

A second-order Monte Carlo simulation was run for 1,000 iterations. The cost-effectiveness acceptability shows that screening in primary care has a 99% probability of being cost-effective compared to no screening at a willingness-to-pay threshold of EUR 20,000 per QALY.

Sensitivity analyses across the tested scenarios showed that the ICER for screening does not change significantly. The largest impact on the ICER is driven by changes to the underlying risk of cardiovascular events, particularly ischemic stroke.

4.6 THE ROLE OF NT-PROBNP IN SCREENING

The role of NT-proBNP in AF screening was evaluated among the participants in study I. Newly detected AF cases had higher NT-proBNP levels (median 335 ng/L (IQR (129, 575)) than individuals with no detected AF (146 ng/L (IQR 77, 239)), $p = 0.033$). Furthermore, patients with known AF had a higher NT-proBNP level (median 697 ng/L (IQR 344, 1508)) compared to newly detected AF cases and individuals with no detected AF ($p = 0.026$ and < 0.001 , respectively) (Figure 12).

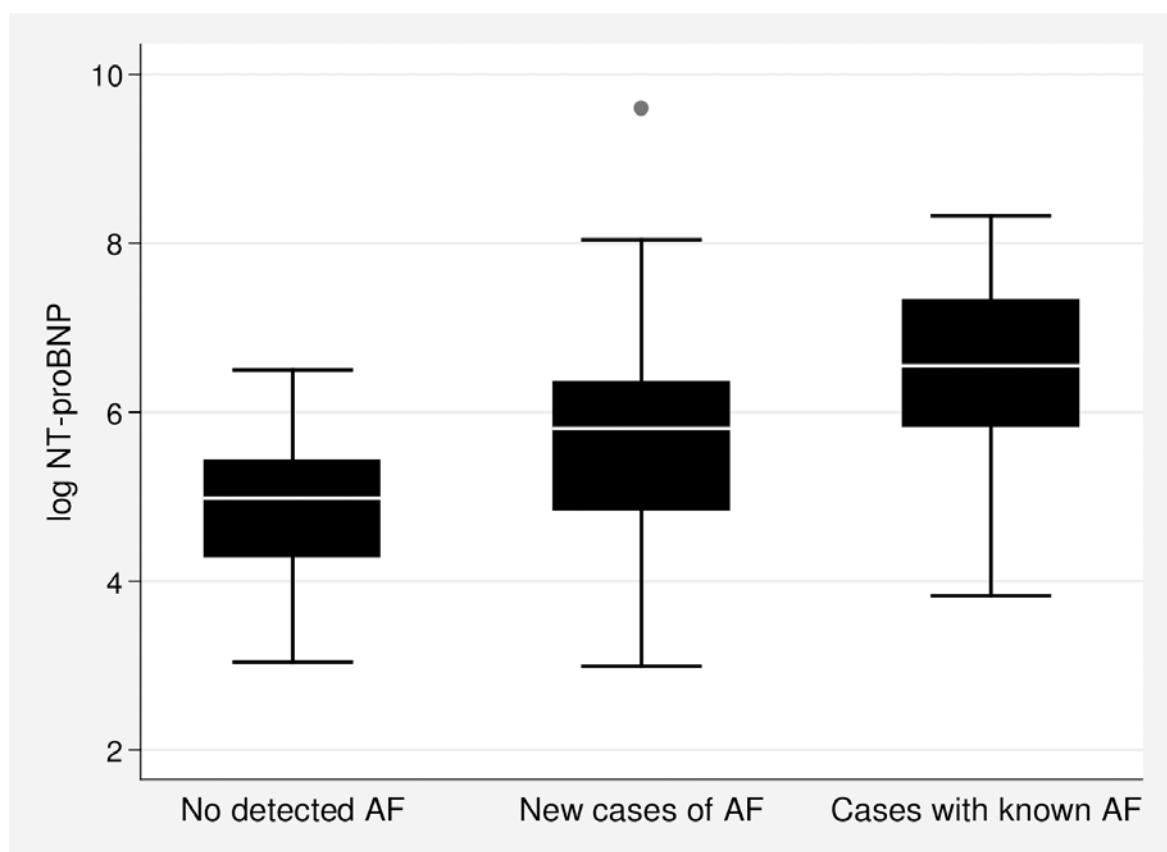


Figure 12. Box plot showing natural logarithm-transformed NT-proBNP values for different AF groups. Reprinted courtesy of Ghazal F et al. (2019) Assessment of N-terminal pro-B-type natriuretic peptide level in screening for atrial fibrillation in primary health care. <https://doi.org/10.1371/journal.pone.0212974>.

The AUC for discrimination of newly detected AF for NT-proBNP was 0.68 (95% CI 0.56 to 0.79) (Figure 13). Screening tests should be sensitive. Thus, we considered 75% minimum sensitivity to determine a cut-off level for NT-proBNP for AF screening. This resulted in a cut-off of 124 ng/L with a specificity of 45% and a negative predictive value of 86%. In AF screening using this cut-off value, 41% of the patients would not have had to undergo

screening by intermittent ECG while missing to detect 25% of AF cases. If Youden's index had been used instead to find the optimal cut-off for NT-proBNP, this would have resulted in a NT-proBNP cut-off value of 570 ng/L with a low sensitivity of 31%.

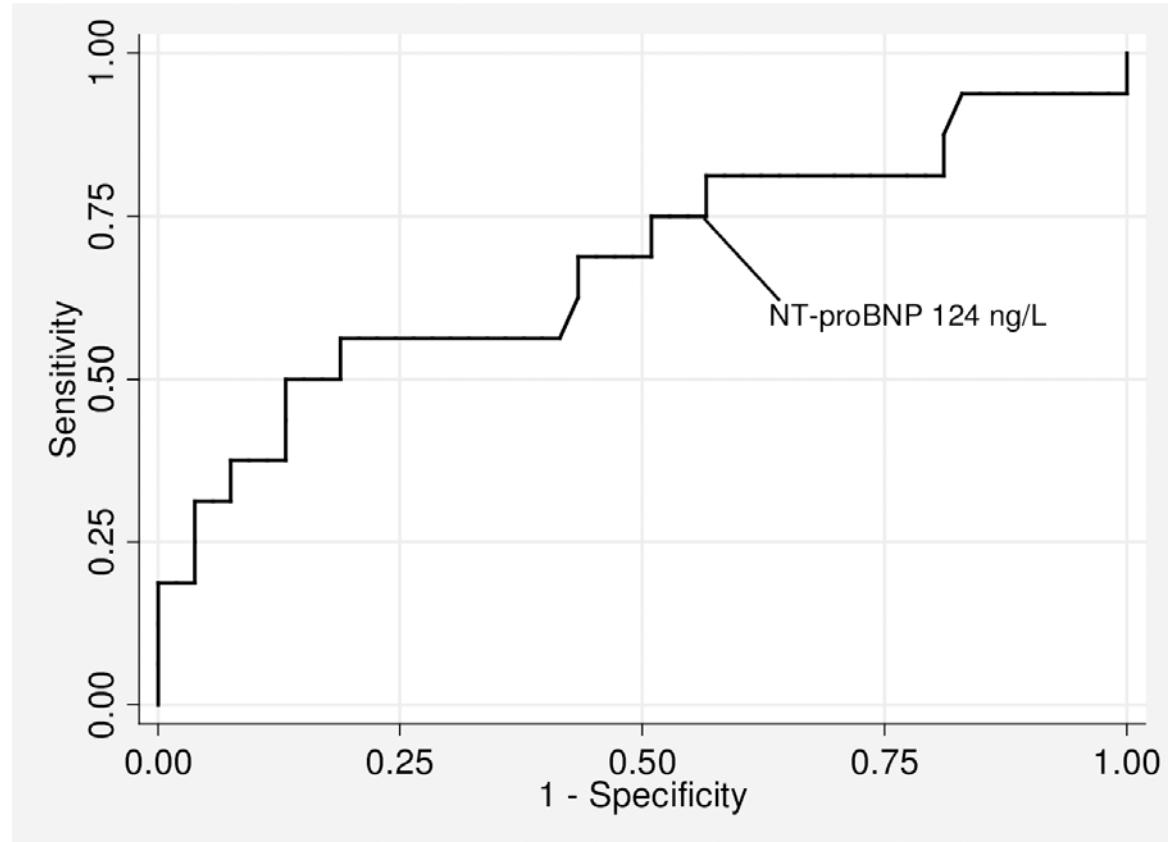


Figure 13. Receiver operating characteristic curve of NT-proBNP plasma level for the detection of new cases of atrial fibrillation. Reprinted courtesy of Ghazal F et al. (2019) Assessment of N-terminal pro-B-type natriuretic peptide level in AF screening in primary health care. <https://doi.org/10.1371/journal.pone.0212974>.

4.7 VALIDITY OF SELF-PULSE PALPATION IN SCREENING

In study IV, a total of 53,782 simultaneous ECG recordings and pulse measurements were registered for the 1,010 screened individuals, corresponding to a median of 51 recordings/individuals. Of the 27 detected AF cases, AF was verified in 311 ECG recordings (Tables 7 A and B) but the pulse was palpated as irregular in only 77 of these recordings, yielding a 25% (95% CI 20 to 30%) sensitivity and a 98% (95% CI 98 to 98%) specificity per measurement occasion (Table 8).

Table 7. (A, B and C) Contingency tables comparing pulse results with ECG results. Reprinted courtesy of Ghazal F et al. (2020) Validity of daily self-pulse palpation for atrial fibrillation screening in patients 65 years and older: A cross-sectional study. PLoS Med.

Table 7 A	AF 27 individuals	No AF 983 individuals
Irregular pulse – 202 individuals	15	187
Regular pulse – 808 individuals	12	796
Table 7 B	AF 311 measurements	No AF – 53,471 measurements
Irregular pulse 1,046 measurements	77	969
Regular pulse 52,736 measurements	234	52,502
Table 7 C	AF 5 individuals	No AF – 1,005 individuals
Irregular pulse – 25 individuals	4	21
Regular pulse – 985 individuals	1	984

Of these 27 AF cases, 15 cases felt an irregular pulse on at least one occasion resulting in 56% (95% CI 35 to 75%) sensitivity per individual (Table 8). 187 individuals without AF felt an irregular pulse on at least one occasion with 81% (95% CI 78 to 83%) specificity and the positive predictive value was 7%.

Pulse palpation by a nurse on inclusion was irregular in 25 cases and five new AF cases were detected on inclusion in which the pulse was irregular in four of the cases (Table 7C) (95% CI 5 to 36%) positive predictive value (Table 8).

Table 8. Validity results of pulse palpation in detecting AF. Reprinted courtesy of Ghazal F et al. (2020) Validity of daily self-pulse palpation for atrial fibrillation screening in patients 65 years and older: A cross-sectional study. PLoS Med.

Variable	Pulse palpation by a nurse on inclusion vs. single ECG measurement		At least one irregular pulse by individual self-pulse palpation under two weeks vs. at least one ECG recording with AF		Individual self-pulse palpation vs. simultaneous ECG	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Sensitivity, %	80	28.36–99.49	55.56	35.33–74.52	24.74	20.06–29.94
Specificity, %	97.91	96.82–98.7	80.98	78.38–83.39	98.19	98.07–98.3
Positive predictive value, %	16	9.39–25.94	7.43	5.29–10.32	7.36	6.09–8.88
Negative predictive value, %	99.9	99.42–99.98	98.51	97.75–99.02	99.56	99.53–99.58

5 DISCUSSION

5.1 PARTICIPATION

The overall participation rate in study I was 78.1%, including previously known AF patients and 76.1%, excluding previously known AF patients. This rate is higher than the participation rate of 54%(34) and 64%(99) in previous systematic community-based AF screening using the same ECG techniques and compared to a 57% participation rate in a systematic screening study(97) in PHC using single time-point ECG, whereas 94% of those participants invited to the opportunistic AF screening study(100) in PHC participated and completed the screening using the same handheld ECG technique.

Although study I was planned to be a systematic screening, it developed into an opportunistic screening in which we invited most of the target individuals directly when they attended PHCC. In this setting, 90% participated in the screening, whereas only 37% of those participants who were invited by post took part. Thus, opportunistic AF screening via invitation when patients attend PHC may be a promising strategy for increasing screening uptake rates. Patients with chronic diseases attend PHCCs regularly. This usually results in better patient-physician relationships and subsequently increased adherence to the physician's recommendations in response to AF screening, as well as adherence to OAC in cases of AF. In study I, participants had higher cardiovascular morbidity than non-participants.

We have no real data on the participation rate in study IV as there were no data on the number of invited individuals for screening among those individuals who attended the PHCCs. However, the research nurses in these centres estimated that more than 80% of the invited individuals were screened. Although the majority of the target population visited their PHCCs during the screening period, only a minority of these patients were invited to the screening. Participation appears to depend more on the availability of health staff and their motivation rather than the motivation of the target population.

Compared to the Swedish general population in the target age (<http://www.statistikdatabasen-scb.se/pxweb/en/ssd/>), the screened individuals were relatively younger and primarily comprised females. Thus, we would probably have detected more AF cases if the participants had corresponded more to the Swedish age and gender distribution.

5.2 ATRIAL FIBRILLATION DETECTION AND ITS PREDICTORS

AF detection rate was 5.5% in study I compared to 2.7% in study IV. Compared to the participants in study IV, the participants in study I (excluding known AF patients) had more prevalent HT, higher SBP, higher BMI and more male gender, but were younger (Table 9). The higher morbidity rate and greater number of male participants in study I could explain the difference in AF detection. The AF detection rate in study IV was comparable to the AF detection rate of 3% in the STROKESTOP(34) study using the same intermittent ECG

technique in a population that was three years older. Thus, our results suggest that AF screening in PHC is promising.

Table 9. Comparison between participants in study IV and study I (excluding patients with known AF)

	Study IV 1,010 participants	Study I 290 participants	P-value*	P-value**
Age, mean year (SD)	72.8 (5.3)	71.9(1.4)	0.0019	0.001
Male (%)	38.4%	46.6%	0.013	0.023
Hypertension (%)	56.7%	75.9%	0.0000	<0.001
Myocardial infarction and/or peripheral artery disease (%)	7.6%	12.8%	0.006	NS
Diabetes (%)	17.6%	22.4%	0.065	NS
Congestive Heart failure (%)	1.5%	2.8%	0.147	NS
Stroke and/or TIA (%)	7.9%	7.2%	0.70	NS
BMI, mean kg/m ² (SD)	26.5 (4.3)	27.4 (4.9)	0.0009	0.017
BP, mean mmHg (SD) Systolic	140.5 (17.9)	146.3 (21.5)	0.0000	<0.001
	Diastolic	83.3 (9.8)	82.8 (12)	0.42
				NS

*Unadjusted comparison between participants in study I and participants in study IV

**Multivariate regression analysis for the participants in study I versus the participants in study IV

Around 20% of all detected AF cases in both study I and study IV were detected at inclusion using single time-point ECG recording. Previous studies(34, 99) reported a similar AF detection rate of 20% at inclusion using single time-point ECG recording related to AF detection using intermittent ECG over two weeks. These results confirm the advantage of using intermittent ECG over two weeks for detecting more AF cases.

A previous systematic screening(95) study in the community using single time-point ECG reported a post screening AF prevalence of 10.8% among 70–74-year olds. In study I, the pre-screening prevalence of 8.2% in this age group increased to 12% by screening using two-

week intermittent ECG. This, in turn, confirms the benefit of intermittent ECG over single time-point ECG for AF screening.

Among the newly detected cases of AF, 75% and 59% were classified as asymptomatic AF in study I and study IV, respectively. These results are comparable to the results of a previous screening study(95) which showed that 65.3% of newly detected AF cases were asymptomatic. Another study(135) reported that 49.5% of AF recurrence in AF patients was asymptomatic.

Paroxysmal AF constituted 62.5% and 92.5% of detected AF in study I and study IV, respectively. The majority of patients who attended the PHCC participated in study I. Thus, almost all of the detected AF cases during the screening period were detected by screening and only one case was detected outside of screening, while in study IV, a minority of those patients who attended the PHCCs were invited to the screening. Thus, probably most patients with non-paroxysmal AF were detected by usual care outside of our screening, resulting in a high proportion of paroxysmal AF detected by our screening. However, a stepwise AF screening study(99) using intermittent ECG over two weeks reported 75% of newly detected AF as paroxysmal.

Predictors of AF

Newly detected AF cases in our screening studies appear to be generally as healthy as individuals without AF. However, age and male gender were independent predictors of AF detection in study IV. This confirms previous evidence(136) that age and male gender is a strong predictor of AF. We studied many morbidities and risk factors for AF detection in study I but the studied age range was restricted and the sample size was small. Thus, we found no association between age and detected AF cases. However, NT-proBNP level and DBP were independent predictors of AF prediction. The role of NT-proBNP in AF detection has been previously verified(69). There is a controversy surrounding the role of DBP in AF detection. However, a nationwide cohort study(137) showed a significant association between incident AF cases and diastolic blood pressure. Undiagnosed HT or undertreated HT may increase the risk of AF. Thus, AF screening for patients with high blood pressure could be considered.

In study I, we also studied the association between known AF and those participants without AF and new AF cases. Patients with known AF were characterized by higher morbidity such as CHF, stroke, COPD, renal impairment, obesity and high NT-proBNP level. CHF was the independent factor associated with known AF. Although CHF is a risk factor for AF, CHF itself could be the result of AF progression. Patients with known AF had more prevalent non-paroxysmal AF than new AF cases. AF usually manifests as paroxysmal AF in the early stages of the disease and then progresses to persistent AF(2). Thus, patients with known AF

may present a late stage of AF progression. Therefore, early detection and management of AF could delay AF progression.

In study I, we also screened for HT and DM and detected 10.2% and 2.5% new cases, respectively. In study IV, around one half of the participants had SBP >140 mmHg. HT and DM increase the risk of stroke in AF patients. Thus, integrating the detection and management of these diseases in AF screening could decrease AF progression and stroke risk. Such integration may be more appropriate in opportunistic AF screening in PHC than community-based systematic AF screening.

5.3 ANTICOAGULANT TREATMENT AND ADHERENCE

Anticoagulation could be initiated by primary care physicians in 92% and 96% of newly detected AF cases in study I and study IV, respectively. This high initiation rate was similar to the STROKESTOP study(34). At the three-year follow up of AF cases detected in study I, adherence to OAC reached a high of 92%. This is comparable to the results of previous screening studies(130) in which the five-year follow-up after AF screening showed an 85% adherence to OAC. Although there have been many AF screening studies globally, few of them have examined the initiation and compliance of AC therapy.

Our results may indicate that there is competence in PHC to initiate OAC and follow-up patients. These results may encourage the initiation of a national screening programme for AF in PHC.

5.4 SAFETY OF SCREENING

At the present time, no screening studies with follow-up regarding the effects on stroke and mortality have been conducted. However, prospective studies (34, 130) are ongoing. Although the screening in study I was not designed to evaluate stroke prevention, the safety results at the three-year follow-up (study III) showed no stroke or severe bleeding. There was no difference in the mortality rate between new AF cases and those cases without AF. This could be related to the similar low morbidity in these groups. It could be also attributed to stroke prevention by early detection of AF and treatment with OAC. The higher mortality rate among patients with known AF could be related to higher morbidity in these patients than the others two groups. Thus, our results suggest that AF screening appears to be safe.

5.5 THE COST-EFFECTIVENESS OF SCREENING

The results of study III demonstrated that AF screening among 70–74-year-olds using Zenicor intermittent ECG in a primary care setting is cost-effective using traditional willingness-to-pay thresholds. This is based on an incremental cost-effectiveness ratio of

EUR 2,389 per gained QALY when a model using three-year follow-up results and extrapolation was used.

If the findings from our study were extrapolated to the Swedish general population in the target age group, this would translate to the detection of 21,731 new AF cases and gain 20,373 QALYs at a cost of EUR 80.5 million. AF screening has been shown to be cost-effective in a number of settings and using different type of screening techniques(112–119).

Mass AF screening(112) among 75–76-year olds in the Swedish population using the same intermittent ECG technique showed an incremental cost of EUR 4,313 per gained QALY. Thus, our results showed a similar cost-effectiveness of AF screening in PHC mainly due to a higher AF detection rate. Although AF screening using intermittent ECG is costly, it detects five times more AF cases than screening using single time-point ECG. A simulation analysis(133) in a hypothetical cohort at 75 years of age showed that AF screening using intermittent ECG is more cost-effective than screening using single time-point ECG.

Community screening for atrial fibrillation using single time-point iPhone ECG in pharmacies in Australia reported a cost of EUR 3,142 per gained QALY in a population with a mean age of 79 years(118), while an AF opportunistic screening study(116) in PHC in The Netherlands using another handheld ECG device (MyDiagnostick) as a single time-point during influenza vaccination reported a cost of EUR 764 per gained QALY in a population with a mean age of 69 years. Finally, a Belgian national campaign for AF screening(132) using a single time-point handheld ECG (Omron HeartScan) reported a cost of EUR 17,693 and EUR 6,708 per gained QALY in a population aged >65 year and >75 years, respectively.

Hence, our study is an important addition to the current situation in which decision-makers and policymakers are attempting to identify the most clinical and cost-effective strategy for AF screening. This study shows that screening in primary care should be considered along with other strategies. Further studies are needed to identify the most suitable strategy regarding who should be screened, in what setting, and when.

5.6 THE ROLE OF NT-PROBNP IN SCREENING

The results of study II confirm the results of a previous screening study(69) using the same intermittent ECG technique among 75–76-year olds, showing that NT-proBNP levels were 472 ng/L, 330 ng/L and 171 ng/L among patients with known AF, newly detected AF and no AF, respectively.

The previous AF screening study(69) reported NT-proBNP level and obesity as independent predictors of AF detection while, in our study, NT-proBNP level and diastolic blood pressure were independent predictors of AF detection. The studied age range in both studies was restricted. NT-proBNP is an independent predictor of the development of cardioembolic

stroke(43, 88). Thus, NT-proBNP can be used for AF detection and as a risk assessment for the development of stroke.

The AUC for AF detection was 0.68 for NT-proBNP in our study versus 0.64 in the previous screening study(69). A 75% sensitivity to AF detection resulted in a cut-off of 124 ng/L in our study. This cut-off level was almost identical to the cut-off of 125 ng/L in the previous study(69) and the specificity was similar at 45%.

In our study, patients with known AF already detected by usual care had more prevalent CHF than AF cases detected by our screening. Patients with known AF had more persistent/permanent AF than AF cases detected by our screening. The progression of paroxysmal AF into persistent/permanent AF is associated with increasing NT-proBNP, progression to CHF and increased comorbidities such as stroke. Thus, early AF detection by screening and early preventive measures could delay the progression to CHF and associated comorbidities.

5.7 VALIDITY OF SELF-PULSE PALPATION IN SCREENING

The role of self-pulse palpation has previously been evaluated on an anatomical model only(77). Our analysis in study IV that compared self-pulse palpation with simultaneous ECG measurements on each occasion showed a low sensitivity to AF detection. Individual analysis based on repeated pulse palpation increases sensitivity to 56%. This sensitivity may be not sufficiently high but using such stepwise screening could save resources by increasing the AF yield. We detected one AF case in 13 individuals through repeated self-pulse palpation compared to detecting one AF case in 37 individuals irrespective of pulse palpation.

Our analysis based on a nurse checking the pulse as a single measure in the PHCCs showed a higher sensitivity of 80% for AF detection on inclusion. A meta-analysis(67) of such pulse palpation showed a higher sensitivity of 92% (95% CI 85 to 96%). However, it is difficult to detect most paroxysmal AF cases through such single-time measurements. We detected only 19% of all new AF cases using initial single ECG measurements at the PHCCs upon inclusion. Repeated pulse palpation (even with low sensitivity) detected more AF cases than single time-point pulse palpation (15 vs. four cases). Repeated self-pulse palpation at home is easy, inexpensive and does not require special equipment.

A meta-analysis(67) for AF detection by single pulse measurement using a smartphone device showed the highest sensitivity of 97% (95% CI 95 to 99%) and a recent study showed comparable sensitivity(72, 138). Again, it is difficult to detect most paroxysmal AF using this single-time-point pulse palpation. Moreover, such screening requires a smartphone. A handheld single-lead ECG connected to a smartphone (72, 138) can be used for AF screening without the need for pulse evaluation. Thus, if such a smartphone ECG is available, repeated measurements could be a sensitive screening method for AF without pulse checking.

5.8 METHODOLOGICAL CONSIDERATIONS

In the following section, the validity of the results of our studies will be discussed. This includes sources of potential bias and how these could influence our results.

5.8.1 SELECTION BIAS

In study I, all individuals in the target population were invited to participate in the AF screening. All participants in study I were then included in study III. This decreased the risk of selection bias in these studies. In study II, all participants in study I with known AF and newly detected AF were included. A non-random sample of participants in study I with no AF was assessed for NT-proBNP and included in study II. This could lead to selection bias in this group. However, there were no statistically significant differences regarding demographical and clinical variables between those participants who were assessed for NT-proBNP and those who were not.

In study I, participation among care-seeking patients was higher than those not seeking care. As the participants had a higher morbidity than the non-participants, this could cause selection bias, so-called participation bias or volunteer bias. This bias could result in an overestimation of AF detection among the participants with high morbidity. However, this could justify opportunistic screening of care-seeking patients rather than systematic screening.

A minority of care-seeking patients in study IV were invited to the opportunistic AF screening. This could lead to some selection bias (referral bias). Compared to the general Swedish population, participants in this study were relatively younger and predominantly female. Research nurses in the PHCCs probably preferred to avoid inviting older individuals with disabilities and high morbidity such as dementia, CHF and COPD. This could result in less AF detection. However, we detected 2.7% new AF cases and would probably have detected a higher proportion of AF if we had screened older people representing the general Swedish population.

In both study I and study IV, the initiation rate of AC was high. This could be due to volunteer bias that the participants were more interested in AF detection and treatment with AC for stroke than those who did not participate. Moreover, physicians at the research PHC could be more motivated to use AC treatment to prevent stroke in AF patients than physicians in general. This is also volunteer bias.

Another type of selection bias in the screening studies is length time bias, i.e. we may have detected more cases of less progressive non-fatal AF and missed cases of progressive fatal AF that would usually have been detected by acute hospital care. This type of bias could be evaluated in randomised control screening studies.

Loss of follow-up bias could affect cohort studies. Study III was a cohort study, while the other studies were cross-sectional studies. In study III, all participants were followed up, resulting in no such bias.

5.8.2 INFORMATION BIAS

Misclassification bias could occur as a result of an unclear classification of the exposures or the outcome. In studies I, II and IV, the outcome was AF and the exposures comprised multiple demographic and clinical characteristics. AF was well defined according to ESC guidelines. We also used well-defined diagnostic criteria for DM, HT and other morbidities. In study III, the outcome was the mortality rate detected from patient registers as a reliable source of information. Thus, there is a low risk of such bias in our studies.

Recall bias is usually associated with case control studies. Thus, there is a minimum risk of such bias as we conducted no case control studies.

Observation bias arises when a researcher collects information about the study population incorrectly. This bias is serious as it could result in differential bias. The outcome of our screening studies was AF detection. The main author was responsible for interpreting the ECG recordings. When the ECG findings indicated AF, the ECG was re-examined by at least one cardiologist to confirm the AF diagnosis. Patients with unclear ECG recordings were further investigated using continuous ECG monitoring. Thus, there is low risk of bias in AF detection. We evaluated many demographic and clinical risk factors for AF detection in various ways, including interviewing the participants, reviewing their medical records and clinical examination. Collecting information in these different ways decreases the risk of observation bias. Moreover, there is no reason to suspect that the observation caused differential bias because data on the exposures were collected before AF detection. Thus, we may have underestimated the association between AF and its risk factors but not overestimated such an association.

The participants' plasma level of NT-proBNP in study I was subsequently retrieved from the patients' medical records in study II. This decreases the risk of observation bias for the association between NT-proBNP and AF. The responsible researcher systematically reviewed all medical records in order to follow-up the participants in study I for mortality, incidental stroke and bleeding. This minimized the risk of observation bias.

Lead time bias is a common problem in screening studies with follow-up analyses. In our cohort study III, we found increased mortality among AF cases detected previously by usual care (known AF) while there was no increase in mortality among screening-detected AF cases. This increased mortality is probably attributable to the fact that we detected AF cases earlier in the disease stages than late stage AF cases detected by usual care. This type of bias could be evaluated in randomized control screening studies.

5.8.3 CONFOUNDING AND CAUSATION

Many risk factors for AF could be confounders or mediators. Thus, we used multiple regression analysis to adjust for potential confounders. Through such analysis in study II, we found that only NT-proBNP and DBP (not GFR and sleep apnoea) were independent

predictors of AF. By using multiple regression analysis in study IV, we found that only age and male gender were predictors of AF detection.

As the sample size in studies I–III was small, we probably missed some associations. We also could not adjust for many variables in these studies due to the small sample size. Although the sample size was larger in study IV, we studied fewer risk factors for AF in this study. Unmeasured confounding cannot be excluded and may have contributed to AF prediction. It would have been interesting if we had studied and adjusted AF detection for echocardiographic variables as potential confounders.

As our studies were cross-sectional, it was difficult to establish a temporal relationship between AF and its predictors (or its consequences). For example, it was difficult to demonstrate whether CHF was a predictor of AF or a consequence of AF.

5.8.4 SIMULATION ANALYSIS

The cost-effectiveness analysis in study III was based on a computer simulation using a Markov method. The results are therefore indicative. Thus, our cost-effectiveness analysis depended on the screening results of study I, its follow-up results and, like most modelling studies, on data from previous studies and assumptions. These clinical and cost data included AF prediction, stroke prediction in treated and untreated patients with AC, cost of stroke care, as well as cost of AC treatment. The validity of our cost-effectiveness results therefore depends on the validity of these data and assumptions.

5.8.5 SAMPLE SIZE

The sample size of the studied population in studies I–III was relatively small. Thus, the statistical power was low for detecting associations detected by previous studies between AF and many risk factors. For example, we reported an increased proportion of HT and DM among AF patients but the associations with AF were statistically non-significant. Moreover, the examined age range was restricted for detecting an association between age and AF. In study III, we found no association between mortality among the detected AF cases versus cases of no detected AF. This is probably a result of AF screening and AC treatment but could also depend on low power (due to the small sample size) in detecting significant associations between mortality and detected AF. However, we detected higher mortality associated with patients with known AF. Moreover, in studies I and II, we could still detect statistically significant associations between AF and many risk factors such as a high level of NT-proBNP, high DBP and many comorbidities.

The studied sample size in study IV was larger and the studied age range was wider. Thus, we were able to detect the associations between AF and age, male gender and CHF.

5.8.6 GENERALIZABILITY

Studies I–III were performed at a single PHCC. This is likely to affect the generalizability of the results to a Swedish general population. The age and gender distribution of the target population in this centre corresponded to the age and gender distribution in the Swedish general population. There is no apparent reason why the results of the studies in this PHCC would differ if implemented in other Swedish PHCCs.

Study IV was a multicentre study. It was implemented in four PHCCs in four different geographic areas in Sweden. Thus, this study would be more representative of the Swedish PHC population and could yield more generalizable results. The age proportion of the target population in these centres was comparable to the corresponding age of the Swedish general population. However, these study centres were non-randomly selected. This, in turn, could affect the generalizability of the screening results.

The NT-proBNP cut-off of 124 ng/L for AF detection derived in study II has not been validated in the same study. Usually, a cut-off point derived in one population must be validated in another population. However, a previous AF screening study(69) showed a similar cut-off of 125 ng/L.

6 CONCLUSIONS, IMPLICATIONS AND FUTURE PERSPECTIVES

Participation in the AF screening programme in PHC using intermittent ECG was high, particularly when the patients attended the PHCCs. Participation appears to depend more on the capacity of health staff to screen rather than the patients' motivation.

AF detection using intermittent ECG over two weeks was five times higher than detection using single time-point recording. Age, male gender, high diastolic blood pressure and high level of NT-proBNP were associated with AF detection. Many new cases of HT and/or DM could also be detected by integrating such screenings with AF screening.

AC treatment (mostly non-vitamin K oral anticoagulants) could be initiated by a general practitioner in almost all newly detected AF cases. AC adherence was high at the three-year follow-up.

AF screening in primary care and initiation of AC among the detected AF cases appears to be safe at the three-year follow-up, in which no increase in mortality or significant bleeding were observed.

AF screening in primary care among 70–74-year-old patients versus no screening appears to be cost-effective using traditional cost-effectiveness thresholds.

The NT-proBNP level was related to AF detection and previous known AF. A cut-off point of 124 ng/L showed a high sensitivity to AF detection, while self-pulse palpation showed a low sensitivity to AF detection.

Thus, we recommend using intermittent ECG as opportunistic AF screening in PHC and to initiate AC therapy among detected AF cases to prevent stroke. Such screening could be more effective for patients aged over 70 years and for those patients with NT-proBNP >124 ng/L. For stroke prevention, it is suggested to integrate screening for other risk factors such as HT and DM with AF screening. The ESC guidelines on AF screening using pulse palpation may need to be updated by replacing pulse palpation with other techniques.

There is a need to evaluate AF screening for stroke prevention through randomized control trials, probably in PHC. The cost-effectiveness of AF screening in such trials could also be evaluated.

7 SWEDISH SUMMARY

SAMMANFATTNING PÅ SVENSKA

SYFTE OCH METOD

Syftet med denna avhandling var att utvärdera resultaten av två tvärsnittsstudier av förmaksflimmer (FF) i primärvården, där man använt intermittent EKG tre gånger dagligen under en tvåveckorsperiod. Målpopulationen i den första studien var alla 70–74 år gamla individer som var inskrivna vid en enda vårdcentral, medan målpopulationen i den andra studien var patienter som var 65 år eller äldre och besökte någon av fyra vårdcentraler. Resultaten var graden av upptäckt av nya FF-fall och graden av insättning av behandling med oral antikoagulantia (OAK) för att förhindra stroke. I den första screeningstudien undersökte vi också vilken roll NT-proBNP har för upptäckt av nya FF-fall. Dessutom bedömde vi säkerheten för den första screeningen vid 3 års uppföljning samt kostnadseffektiviteten för screeningen. Slutligen studerade vi validiteten för självpalpation av puls jämfört med samtidig EKG-registrering för upptäckt av FF.

RESULTAT

Studie I: Målpopulationen blev inbjuden till screening vid besök i primärvården under en tiomånadersperiod. De som inte hade kontakt med vårdcentralen under denna period blev inbjudna att delta per brev. Av de 415 tillfrågade individerna deltog totalt 324 (78,1 %) patienter i studien. Medelåldern för deltagarna var 72 år och 52,2 % var kvinnor. I målpopulationen hade 34 (8,2 %) individer tidigare diagnostiserat FF. Bland deltagare utan tidigare känt FF upptäcktes 16 (5,5 %) fall av FF. Den slutliga prevalensen av FF i målpopulationen var 12 %. Behandling med oral antikoagulantia inleddes framgångsrikt hos 88 % av patienterna med nyligen upptäckt FF.

Studie II: Plasma-NT-proBNP mättes hos patienter med tidigare känt FF, nyligen upptäckt FF och 53 kontrolldeltagare utan FF. Median-NT-proBNP var 697 ng/L bland patienterna med tidigare känt FF, 335 ng/L i nya fall av FF och 146 ng/L bland patienterna utan FF. Efter justering för flera kliniska variabler och sjuklighet var skillnaderna i median-NT-proBNP-nivåer statistiskt signifikanta mellan fall av tidigare känt FF och nya fall av FF samt mellan nya fall av FF och patienter utan FF. Området under mottagarens operativa karakteristiska kurva för upptäckt av ny FF var 0,68 (95 % CI 0,56 till 0,79), vilket gav ett cut off-värde på 124 ng/L med 75 % känslighet, 45 % specificitet och 86 % negativt prediktivt värde.

Studie III: Medan dödligetsgraden bland patienter med känt FF var högre än bland patienter utan FF (HR 3,6, 95 % CI 1,5 till 8,7), fanns det ingen statistiskt signifikant skillnad i dödliget mellan fall med ny FF jämfört med dem utan FF (HR 0,86, 95 % CI 0,12 till 6,44). Fölsamheten när det gäller OAK var 92 %. Ingen stroke eller svår blödning har upptäckts. Det kostnadseffektivitetsförhållandet för screening jämfört med ingen screening uppgick till €2 389/QALY. I en probabilistisk känslighetsanalys visade screeningen 99 %

sannolikhet för att vara kostnadseffektiv jämfört med ingen screening med en betalningsvillighet på 20 000 € per QALY.

Studie IV: Totalt 1 010 patienter (medelålder 73 år, 61 % kvinnor) deltog i studien och 27 (2,7 %, 95 % CI 1,8 till 3,9 %) nya fall av FF upptäcktes. Antikoagulantia kunde sättas in i 26 (96 %, 95 % CI 81 till 100 %) av dessa fall. Totalt registrerades 53 782 samtidiga EKG-inspelningar och pulsmätningar. FF verifierades i 311 EKG-inspelningar, varav pulsen palperades som oregelbunden hos 77 patienter (25 %, 95 % CI 20 till 30 % känslighet per mätningstillfälle). Av 27 FF-fall kände 15 fall en oregelbunden puls vid minst ett tillfälle (56 %, 95 % CI 35 till 75 % känslighet per individ). 187 individer utan FF kände en oregelbunden puls vid minst ett tillfälle. Specificiteten per mätstillfälle och per individ var (98 %, 95 % CI 98 till 98 %) respektive (81 %, 95 % CI 78 till 83 %).

SLUTSATSER

Graden av upptäckt av ny FF genom dessa screeningsstudier var 5,5 % bland patienterna i åldern 70–74 år och 2,7 % bland patienterna som var 65 år eller äldre. Graden av insättning av OAK var hög (88 % respektive 96 %) och 3 års följsamhet var hög (92 %) i den första screeningstudien. Deltagandet i den första studien var högt (78,1 %) främst via opportunistisk inbjudan. NT-proBNP verkar vara en användbar screeningmarkör för upptäckt av FF och typ av FF medan validiteten för självpalpation av puls för FF-upptäckt var låg. Screeningen verkar vara säker och kostnadseffektiv (€2 389/QALY). Därför kan opportunistisk screening i primärvården genom intermittent EKG (med eller utan NT-proBNP) och insättning av OAK för upptäckta FF-fall förhindra stroke. Det finns emellertid behov av att utvärdera effektiviteten hos ett sådant screeningprogram genom en stor randomiserad studie med flera centra, förslagsvis som opportunistisk screening i primärvården.

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