From the Department of Clinical Sciences

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SCREENING FOR SILENT CARDIAC DISEASE IN AN ELDERLY POPULATION AIMING AT STROKE REDUCTION

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Screening for silent cardiac disease in an elderly population aiming at stroke reduction

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Til elsku stelpnanna minna

"The path is the goal"
Mahatma Gandhi

Abstract

INTRODUCTION

Atrial Fibrillation is the most common clinical arrhythmia and affects over 30 million people worldwide. Atrial fibrillation is a leading cause of morbidity and mortality worldwide with death, stroke and heart failure being the most feared complications. It is a well-known risk factor for stroke, a risk that can be reduced by about two-thirds in high-risk individuals with oral anticoagulant treatment. Atrial fibrillation patients can be asymptomatic, and many individuals-especially the elderly-are unaware that they have atrial fibrillation. Because atrial fibrillation is a common, chronic and often asymptomatic disease, with increased risk of serious but to certain extent preventable complications, it seems to meet most of the World Health Organization's criteria for population screening. Screening for atrial fibrillation and initiation of oral anticoagulant therapy could potentially prevent stroke from atrial fibrillation in high-risk individuals, but the optimal screening program and strategies are not yet defined. Several large-scale, randomised studies are ongoing with the aim to answer the question if we should screen for atrial fibrillation, the STROKESTOP I and STROKESTOP II studies being among them.

AIMS

I. to study atrial fibrillation detection and predictors for new atrial fibrillation by using the biomarker NT-proBNP in a stepwise screening of a high-risk population and to study oral anticoagulant treatment uptake as well as one-year adherence to treatment in individuals diagnosed with new atrial fibrillation during screening.

II. to study atrial fibrillation detection using pulse palpation and compare it to single-lead ECG and to study if symptoms of palpitations are associated with atrial fibrillation yield in screening.

III. to analyse geographic and sociodemographic disparities in the uptake of the STROKESTOP II study and compare the results between STROKESTOP I and STROKESTOP II after the intervention of adding two screening sites in STROKESTOP II.

IV. to study the potential yield of detected disease in non-participants and to compare characteristics of non-participants to participants.

METHODS

In study I all 75/76-year-olds in the Stockholm region (n=28,712) were randomized 1:1 to be invited to participate in the STROKESTOP II study-an atrial fibrillation screening study-or to serve as control group. Participants without previous atrial fibrillation had NT-proBNP measured and were stratified into low-risk group with NT-proBNP <125 ng/L or a high-risk group with NT-proBNP ≥125 ng/L. The high-risk group was offered 2 weeks intermittent ECG-screening whereas the low-risk group performed only one single-lead ECG recording at the screening visit. Participants diagnosed with atrial fibrillation were referred to a cardiologist for assessment and started on OAC unless contraindicated.

In study II the participants from the STROKESTOP II study that did not have prior atrial fibrillation diagnosis were included. Healthcare professionals at the screening visit palpated their radial pulse for 30 seconds and recorded it as regular or irregular. Thereafter a 30-second single-lead ECG was registered. Patients also answered the yes/no question if they had felt palpitations.

In study III data from the intention-to-screen group in the STROKESTOP II study were included and the same data variables from the STROKESTOP I participants was available. In the STROKESTOP II study, two additional screening sites were used compared to in the STORKESTOP I study, closer to low-income neigbourhoods. Invitee's residential parish was used for geo-mapping analysis of the geographical disparities in participation, using hierarchical Bayes methods. Individual data for participants and non-participants were obtained from Statistics Sweden with respect to following socioeconomic variables: educational level, disposable income, immigrant and marital status.

In study IV anonymised individual data for non-participants and participants were obtained from Swedish registries regarding socioeconomic factors, medical history and dispensed medicines. A random forest was trained to predict propensity scores for participation. The propensity scores were used to infer on potential screening yield of disease among non-participants.

RESULTS

In total, 6,868 individuals accepted the screening invitation to participate in the STROKESTOP II study. Participants without prior atrial fibrillation diagnosis were 6,315 (91.9%). New atrial fibrillation was diagnosed in 4.4% (95% CI 3.7-5.1) of the participants in the high-risk group. In all participants without prior atrial fibrillation new atrial fibrillation was detected in 2.6% (95% CI 2.2-3.0). The screening procedure resulted in an increase in known prevalence from 8.1% to 10.5% among

all participants. Oral anticoagulant treatment was initiated in 94.5% of the participants with new atrial fibrillation diagnosis and at one-year follow-up 96% were still adherent to the treatment.

Of the 6,159 participants included in the study II, 461 (7.5%) had irregular pulse. Twenty-two (4.8%) of those with irregular pulse were diagnosed with atrial fibrillation on single-lead ECG rhythm strip. Among those with regular pulse, 6 (0.1%) cases of new atrial fibrillation were found. The sensitivity of the pulse palpation test was 78.6% and positive predictive value 4.8%. The proportion of newly diagnosed atrial fibrillation was not different between those with and without history of palpitations.

Higher participation was observed in those with higher education, high income, among non-immigrants and married individuals in study III. Participation between STROKESTOP I and STROKESTOP II improved significantly where additional screening sites were introduced. These improvements were generally significant, in each population group according to socio-demographic characteristics.

In study IV the atrial fibrillation prevalence was 17.9% among non-participants compared to 8.9% in non-participants. Non-participants were in poorer health, had lower socioeconomic status and were less mobile than participants. The most important factors to predict non-attendance were low income, hospitalisations and higher CHA_2DS_2-VASc scores. The weighted estimates suggested that the estimated yield of untreated AF was 3.6% in non-participants compared to 3.3% in the participants.

CONCLUSIONS

In an NT-proBNP-stratified systematic screening for atrial fibrillation, 4.4% of the high-risk participants were diagnosed with new atrial fibrillation. Oral anticoagulant treatment initiation was well accepted in the group diagnosed with new atrial fibrillation.

Pulse palpation was inferior to single-lead ECG when screening for atrial fibrillation and we would advocate the use of single-lead ECG rather than pulse palpation when screening for atrial fibrillation. Palpitations did not predict new diagnosis of atrial fibrillation.

Decentralisation of screening sites in an atrial fibrillation-screening-program yielded a significantly positive impact on screening uptake. Addition of local screening sites in areas with low uptake had beneficial impact on participation across a wide spectrum of socio-demographic groups. Importantly, decentralised screening increased substantially the screening uptake in deprived areas.

The potential yield of untreated atrial fibrillation detected by screening was esti-

mated higher among non-participants than among participants. The non-participants had higher CHA_2DS_2-VASc scores, underlining their high stroke-risk and probable benefit from attending screening.

.

List of scientific papers

I. Kemp Gudmundsdottir, K, Fredriksson, T., Svennberg, E., Al-Khalili, F., Friberg, L., Frykman, V., Hijazi, Z., Rosenqvist, M., Engdahl, J.

Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study
Europace. 2020 Jan 1;22(1):24-32

II. Katrin Kemp Gudmundsdottir M.D., Tove Fredriksson M.D.,Ph.D, Ph.D., Emma Svennberg, M.D., Ph.D., Faris Al-Khalili, M.D, Ph.D., Leif Friberg, M.D., Ph.D., Henrike Häbel, Ph.D., Viveka Frykman, M.D., Ph.D., Johan Engdahl, M.D., Ph.D.

Performance of pulse palpation compared to one-lead ECG in atrial fibrillation screening
Submitted

III. Gudmundsdottir, Katrin Kemp, Holmen, Anders, Fredriksson, Tove, Svennberg, Emma, Al-Khalili, Faris, Engdahl, Johan, Strömberg, Ulf

Decentralising atrial fibrillation screening to overcome socio-demographic inequalities in uptake in STROKESTOP II
J Med Screen. 2020 Mar 30:969141320908316 (online ahead of print)

IV. Katrin Kemp Gudmundsdottir M.D., Carl Bonander Ph.D, Tove Fredriksson M.D.,Ph.D, Emma Svennberg, M.D., Ph.D., Faris Al-Khalili, M.D, Ph.D., Viveka Frykman, M.D., Ph.D., Ulf Strömberg Ph.D, Johan Engdahl, M.D., Ph.D.

Estimating the potential yield of detected disease among non-participants: an application to a population-based atrial fibrillation screening study
Submitted

Contents

List of abbreviations

AF	Atrial Fibrillation
AHRE	Atrial High Rate Episodes
ATC	Anatomical Therapeutic Chemical
ATE	Average Treatment Effect in the population
ATU	Average Treatment Effect in the Untreated
BNP	Brain natriuretic peptide
BP	Blood pressure
BPM	Blood pressure monitor
ECG	Electrocardiogram
eCRF	Electronic case report form
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
ICD	Implantable cardioverter defibrillator
ICM	Implantable cardiac monitor
ILR	Implantable loop recorder
IPSW	Inverse probability of sampling weights
IQR	Inter quartile range
NOAC	Non-vitamin K antagonist oral anticoagulants
NPR	National Patient register
NT-proBNP	N-terminal pro B-type natriuretic peptide
OAC	Oral anticoagulant
PPG	Photopletysmographic
PR	Participation rates
Q	Quartile
QALY	Quality-adjusted life-year
SCB	Statistikmyndigheten
SD	Standard Deviation
TIA	Transient ischaemic attack
USPSTF	The United States Preventive Service Task Force
VKA	Vitamin K antagonists
WHO	World Health Organization

1 INTRODUCTION

Atrial Fibrillation (AF) is the most common clinical arrhythmia and affects over 30 million people worldwide with a global prevalence that is increasing (1-3). AF is a well-known risk factor for stroke and a major cause of cardiovascular morbidity and mortality (4-6). The combination of increasing prevalence and serious complications of the disease make AF a global health problem and a burden on health care systems around the world, see Figure 1 (7). A non-infectious pandemic, of sorts.

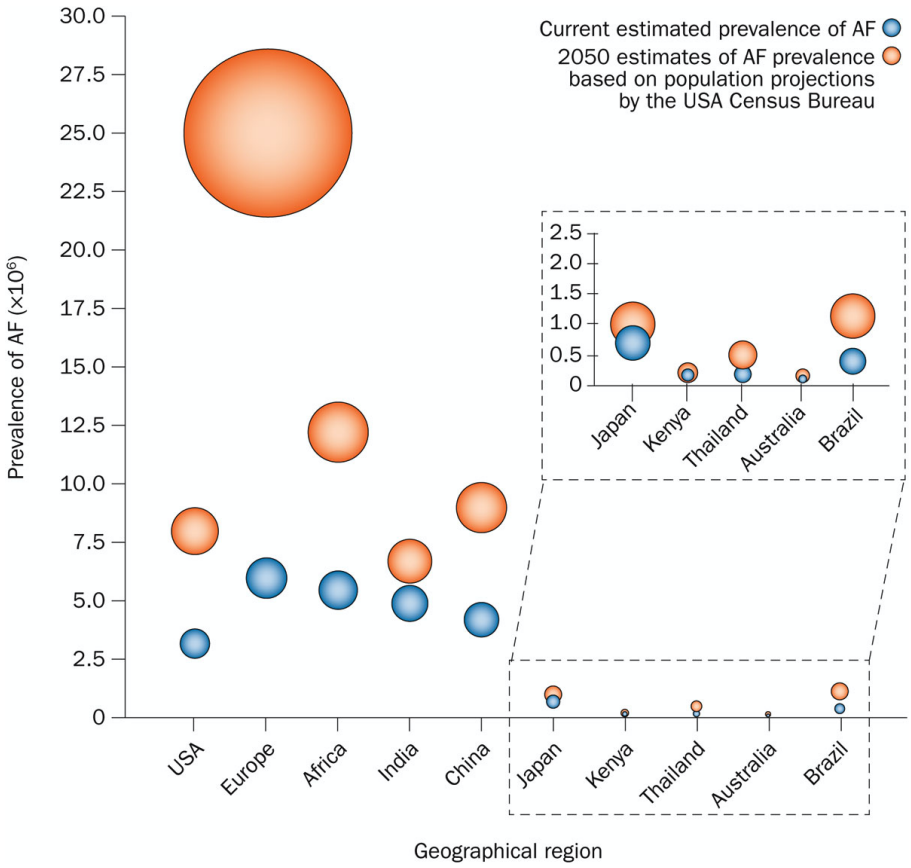

Figure 1. Global prevalence of AF. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nature reviews Cardiology. 2014;11(11):639-54 Reprinted by permission of Springer Nature

The 2020 European Society of Cardiology (ESC) AF Guidelines highlight early diagnosis, integrated patient management as well as prevention as key messages in AF management with the goal to reduce the global disease burden (8).

AF patients can be asymptomatic, and many individuals-especially the elderly-are unaware that they have AF (9, 10). Unfortunately, AF increases stroke risk regardless of symptoms (11, 12). In about 10% of all ischaemic strokes, new AF is only detected at admission (13). Oral anticoagulant (OAC) treatment has been shown to reduce stroke risk by 60-70% in individuals at increased risk (14), and calculating stroke risk and initiation of OAC treatment when indicated is considered one of the most important factors to address when new AF is discovered.

Because AF is a common, chronic and often asymptomatic disease, with increased risk of serious but to a large extent preventable complications, it seems to meet most of the World Health Organization's (WHO) criteria for population screening as defined by the Wilson and Jungner in 1968 (15).

A study screening for AF in elderly subject through pharmacy-based single-lead ECG found that in individuals diagnosed with AF through screening had a significantly higher mortality risk during 1-year follow-up than individuals without new AF (16). In a Swedish AF screening study with 848 participants the stroke incidence in the intervention municipality declined significantly compared to the surrounding control area after five years of follow up (17). This study, however, was non-randomised, making causal inference difficult. An observational study on incidentally detected AF found that OAC treatment reduced both stroke and death, suggesting that AF found by screening would have similar results (11).

Systematic screening for AF is large scale and expensive, making it necessary to study if it reduces stroke and death and if it does, how it can be done cost-effectively for the society. N-terminal B-type natriuretic peptide (NT-proBNP) has been shown to be one of the strongest biomarkers predicting AF development (18) and is associated with increased risk of stroke and mortality in AF patients (19). This combination makes it attractive as a possible aid in identifying those at highest risk for new AF and stroke and possibly at the same time for reducing the cost of systematic screening.

Technologies for detecting irregular pulse and for recording electrocardiogram (ECG) rhythm strips are rapidly developing and could potentially be of practical use when screening for AF. The 2020 ESC AF Guidelines recommend opportunistic screening by pulse palpation or rhythm strip in patients >65 years of age (8). A study showing only 25% sensitivity per measurement compared to single-lead ECG when performed by laymen indicates that pulse palpation is inexpensive but more difficult and less effective than one would think (20). In comparison to several studied tools, such as automated blood pressure (BP) monitors, single-lead ECG, smartphone apps and smart watches pulse palpation has the lowest sensitivity and specificity (21). In

an era with abundance of detection devices using rhythm algorithms, pulse palpation seems like a less suitable option with its low diagnostic performance.

The success of any screening program is dependent on participation. Socio-demographic factors influence participation, with lower income, educational level as well as immigrant status being associated with lower participation rates (22). Lower socioeconomic status is also associated with worse outcome in several cardiovascular diseases, including AF and heart failure (23, 24). It is, therefore, important to study which factors influence screening participation to try to infer on what can be done to reduce this socioeconomic gradient on screening participation and disease outcome.

This thesis focuses on population screening for AF. We studied the yield of stepwise AF screening with the addition of a biomarker and studied the initiation and adherence of OAC treatment in participants with new AF. We compared pulse palpation and single-lead ECG as diagnostic modalities in AF screening. Lastly, we examined what influenced screening participation and aspired to infer ways to increase participation among individuals at the highest risk for AF and stroke in possible future AF-screening scenarios.

2 BACKGROUND

2.1 PRESENT AND PREDICTED EPIDEMIOLOGY OF ATRIAL FIBRILLATION

AF is already the most common sustained cardiac arrhythmia and is expected to reach even higher levels as both prevalence and incidence is on the increase (2). Chugh et al. reviewed population studies from 1980 to 2010 and the estimated number of individuals living with AF in 2010 was 33.5 million; men showed higher prevalence than women, developed countries more than developing countries and older age groups more than younger individuals (2). In Sweden the prevalence in 2010 was 2.9% in the total adult population (>20 years) based on the in-patient covering registries, increasing with age to up to 14.3% at 84 years (25). The range in prevalence is quite large, from 0.2% in adult men <35 years to as high as 15% in men >85 years. A similar trend, albeit less common, was found in women in a 2015 study of on over two million citizens in Israel (26). AF prevalence, however, might be underestimated, as the disease is commonly asymptomatic and often remains undiagnosed (27).

Risk factors such as hypertension and obesity are growing problems worldwide that promote AF and can also influence the incidence (28, 29). As the global population ages, the number of adults living with AF is expected to double in the next 30-40 years, see Figure 2 (3). Apart from an increase in risk factors for AF and a demographic shift, the incidence increase might also lead to increased AF awareness

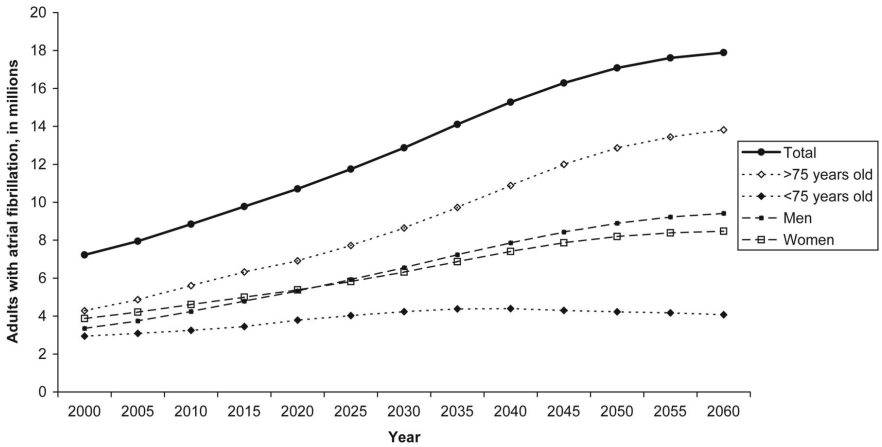

Figure 2. Projected number of adults with atrial fibrillation in the European Union between 2000 and 2060. Krijthe BP et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. European Heart Journal. 2013;34(35):2746-51. Reprinted by permission of Oxford University Press

and more intense pursuit to find new AF (30). The more intensively you look for AF, it seems, the more you find, with new AF detected in 16.1% of patients with a 30-day event-triggered recorder vs. 3.2% on 24h Holter in the EMBRACE trial (31).

It is well known that AF is associated with an increase in mortality (4) as well as an increased risk for stroke and heart failure (5). Common cardiovascular diseases such as hypertension, heart failure, valvular disease, diabetes, obesity and chronic kidney failure are concomitant conditions that increase the risk of developing AF and complications of AF. In recent years there has been a growing interest in the association between AF and cognitive decline, higher risk of dementia (32) and impaired quality of life (33). The health care burden of AF is already considerable with frequent hospitalisations of AF patients (34). The care of AF patients accounts for about 708 million euros in direct and indirect costs annually in Sweden (35), raising concerns that an increase in healthcare expenditures will accompany the predicted amplified prevalence.

Early diagnosis, prevention and treatment of AF along with stroke risk assessment, prevention and treatment of concomitant cardiovascular diseases are important factors in preventing AF and its disease burden in the future (36, 37).

2.2 DIAGNOSTIC CRITERIA AND DEFINITION OF ATRIAL FIBRILLATION

For the diagnosis of AF, a rhythm recording using an ECG is required, see Figure 3. A 12-lead ECG-recording or single-lead ECG recording of at least 30 seconds showing the following ECG patterns: Absolute irregular rate-to-rate intervals and an absence of normal p-waves confirms AF diagnosis (8). The diagnosis of AF is independent of symptomatology.

During AF, atrial activity might be seen on the ECG, but the atrial complexes, termed f-waves, have a different configuration and a variance in distance between the different atrial complexes. The atrial rate during atrial fibrillation is >300 per minute (6).

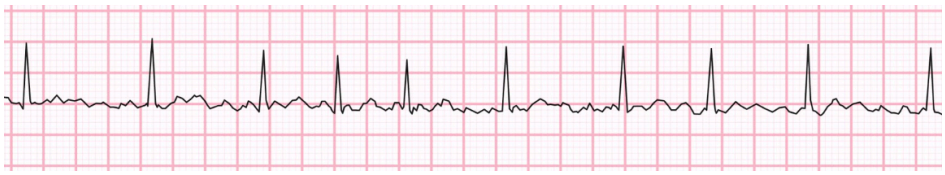

Figure 3. An ECG rhythm recording showing atrial fibrillation

Atrial fibrillation is a chronic and usually progressive arrhythmia and seems to follow a “natural time course” in most cases, see Figure 4 (38). Commonly AF pro-

gresses from short and infrequent episodes to more permanent forms over time, but the progression to permanent forms of AF is low in young and healthy individuals (39).Based on presentation, duration and type of termination, AF is classified into five different groups: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent (8).

- *First diagnosed AF* –AF not diagnosed before irrespective of duration, presence or severity of symptoms.
- *Paroxysmal AF* – AF that terminates spontaneously or with intervention within 7 days. In many cases termination occurs within 48 hours.
- *Persistent AF* – AF that is continuously sustained for more than 7 days and/or if medical or direct current cardioversion is performed to restore sinus rhythm after ≥7 days.
- *Long-standing persistent AF* – when AF lasts for more than one year, and the aim is a rhythm control strategy.
- *Permanent AF* – AF that is accepted by the patient and physician and no further attempts to restore/maintain sinus rhythm.

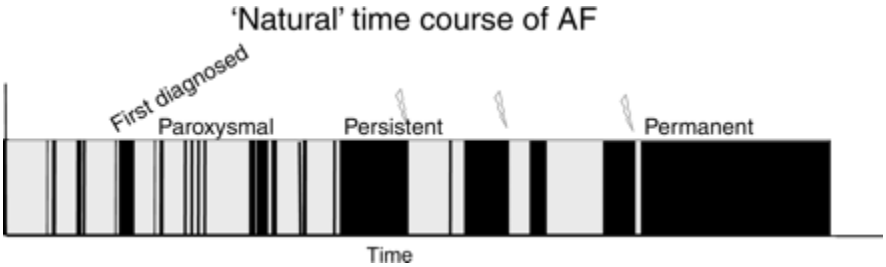

Figure 4. "Natural time course of AF" Kirchhof P et al. Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organised by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. Europace. 2007;9(11):1006-23. Reprinted by permission of Oxford University Press

2.3 HOLISTIC AND MULTIDISCIPLINARY CARE OF ATRIAL FIBRILLATION PATIENTS

The 2020 ESC AF Guidelines stress the importance of integrated AF patient management, with the patient at the center (8). The ABC pathway has been proposed as a way to streamline integrated care for AF patients, where the A stands for "avoid stroke", the B for "Better symptom management" and the C for "Cardiovascular and comorbidity risk reduction", see Figure 5 (41). The ABC pathway creates a simple path for clinicians of different specialties to follow in their management of AF patients and has been shown to lower cardiovascular events compared to usual care (42, 43).

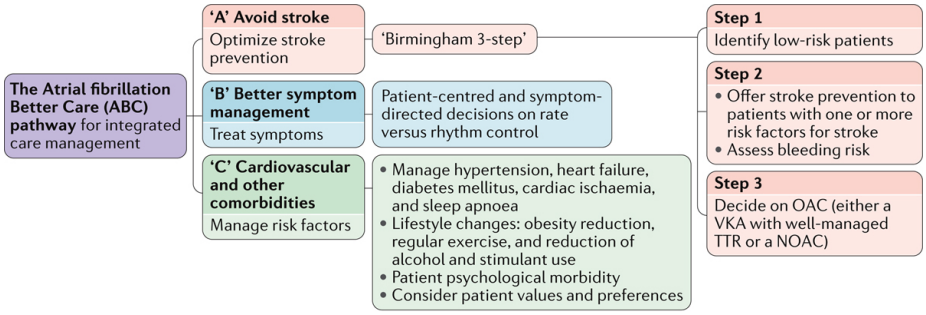

Figure 5. The ABC pathway: an integrated approach to improve AF management Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nature reviews Cardiology. 2017;14(11):627-8. Reprinted by permission of Springer Nature

2.4 STROKE RISK AND ORAL ANTICOAGULANT TREATMENT IN ATRIAL FIBRILLATION PATIENTS

The increased stroke-risk in AF patients has long been established (6). Age, sex and comorbidities of the patient are combined in the widely used CHA_2DS_2-VASc score that predicts those at high risk for stroke (44) and is used in treatment guidance, shown in Table 1.

Risk factors for stroke	Score awarded
Congestive heart failure	1
Hypertension	1
Age ≥75	2
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age ≥65	1
Female sex	1

Table 1. The CHA_2DS_2-VASc score used for assessing the stroke risk in AF patients. TIA indicates transient ischaemic attack. Adapted from Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72

As any clinical risk-factor-based score, CHA_2DS_2-VASc performs only modestly in predicting high-risk patients who will sustain thrombo-embolic events, but those identified as low-risk (CHA_2DS_2-VASc 0 (males), or score of 1 (females)) consistently have low ischaemic stroke or mortality rates (<1%/year) and do not need any stroke prevention treatment. Stroke prevention should be considered in all patients with CHA_2DS_2-VASc of 1 if male, or score of 2 if female and is recommended in patients with CHA_2DS_2-VASc of 2 if male, or score of 3 if female (8). Modifiable

bleeding risk factors should be addressed and a HAS-BLED score calculated to flag up the patient for regular review (45), see Table 2.

	Risk factors and definitions	Points awarded
H	Uncontrolled hypertension (>160mmHg)	1
A	Abnormal renal and/or hepatic function (Dialysis, transplant, serum creatinine>200mcmol/L, cirrhosis, bilirubin>2x upper limit, AST/ALP/ALT>3x upper limit)	1 point for each
S	Stroke (previous ischaemic or haemorrhagic stroke)	1
B	Bleeding history or predisposition (major haemorrhage, anaemia or sever thrombocytopenia)	1
L	Labile INR (TTR <60% in patient receiving VKA)	1
E	Elderly (>65 years or extreme frailty)	1
D	Drugs or excessive alcohol consumption	1 point each

Table 2. The HAS-BLED risk score for bleeding. Adapted from Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138:1093_1100.

The ABC (Age, Biomarkers, Clinical history) stroke risk score is another, more recent, instrument that combines biomarkers with clinical history and has performed better in studies than the CHA_2DS_2-VASc score (46). The ABC stroke risk score nomogram is shown in Figure 6.

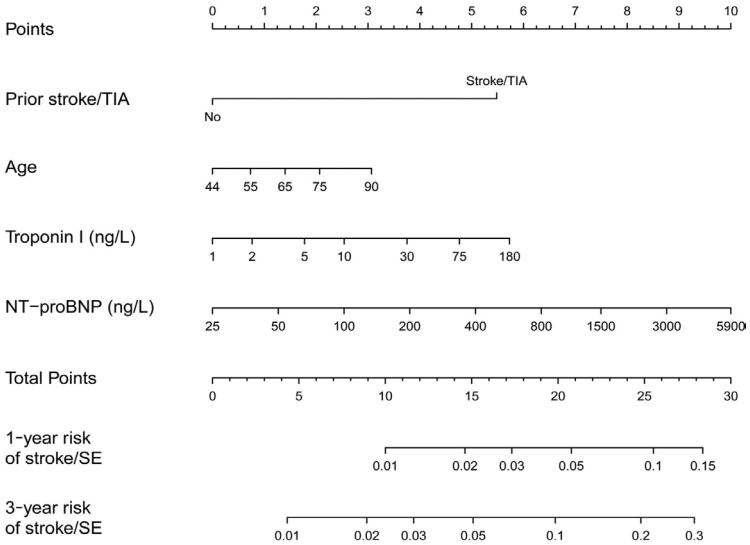

Figure 6. Nomogram for the ACB stroke risk score. Hijazi Z et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. European Heart Journal. 2016;37(20):1582-90. Reprinted by permission of Oxford University Press

More recent studies concentrate on whether factors such as AF duration, burden, type and subclinical AF (AF diagnosed with an opportune ECG in asymptomatic patients) affect stroke-risk in such a way that would change generally recommended anticoagulant treatment recommendations.

The highest risk of stroke and death is found in patients with non-paroxysmal AF (47). Device-detected subclinical AF is common, and any event of subclinical AF >6 minutes increases the annual risk of stroke or peripheral emboli by a factor of 2.5 (48). In patients with paroxysmal AF it seems that the greater the burden of AF the greater the risk of stroke (49).

OAC treatment has been shown to reduce ischaemic stroke by at least two thirds and to reduce mortality in AF patients (14). The CHA_2DS_2-VASc score has been widely used to guide OAC treatment since it was included in the 2010 ESC AF Guidelines (50).

Vitamin K antagonists (VKA), such as warfarin, were the first anticoagulants used in the attempt to reduce stroke risk in AF patients and are still first choice in patients with AF with rheumatic mitral valve disease or mechanical heart valves (51). In the last 10 years, however, the use of Non-vitamin K antagonist oral anticoagulants (NOACs) has been rapidly increasing (52). This is in accordance with evidence supporting efficacy and safety of the NOACs compared to warfarin (53).

With OAC treatment comes increased risk of bleeding. There are several bleeding scores that can be used similarly to the CHA_2DS_2-VASc score to assess the risk of bleeding in patients (45, 54, 55) but the same risk factors that predict stroke are often also the ones that predict bleeding. The 2020 ESC AF Guidelines recommended calculating a HAS-BLED score and to address modifiable bleeding risk factors to flag the patient for a more regular review, instead of withholding OAC treatment (8). Treating modifiable bleeding risk factors such as uncontrolled hypertension, alcohol abuse, anaemia etc. is recommended.

2.5 RISKS AND SYMPTOMS RELATED TO ATRIAL FIBRILLATION

AF is a leading cause of morbidity and mortality worldwide (6, 56) with death, stroke and heart failure (5) being the most feared complications. In world-wide cohort study that included 15,400 patients from 47 countries, it was shown that 11% of patients presenting with AF to the emergency department died within one year, mostly from heart failure, but also from stroke (5).

Heart failure and AF are closely related by their shared pathophysiology and can both cause and exacerbate each other (57, 58). Heart failure is the leading cause of

death in AF patients (5) and as such is an important disease to prevent, find and treat in AF patients.

In patients with AF, there is evidence associated with smaller brain volume (59), accelerated cognitive decline and higher risk of dementia (33, 60) even without history of stroke, a risk which is higher without OAC treatment (61). The 2020 ESC AF Guidelines summarise the clinical presentation of AF and AF-related outcomes in Figure 7.

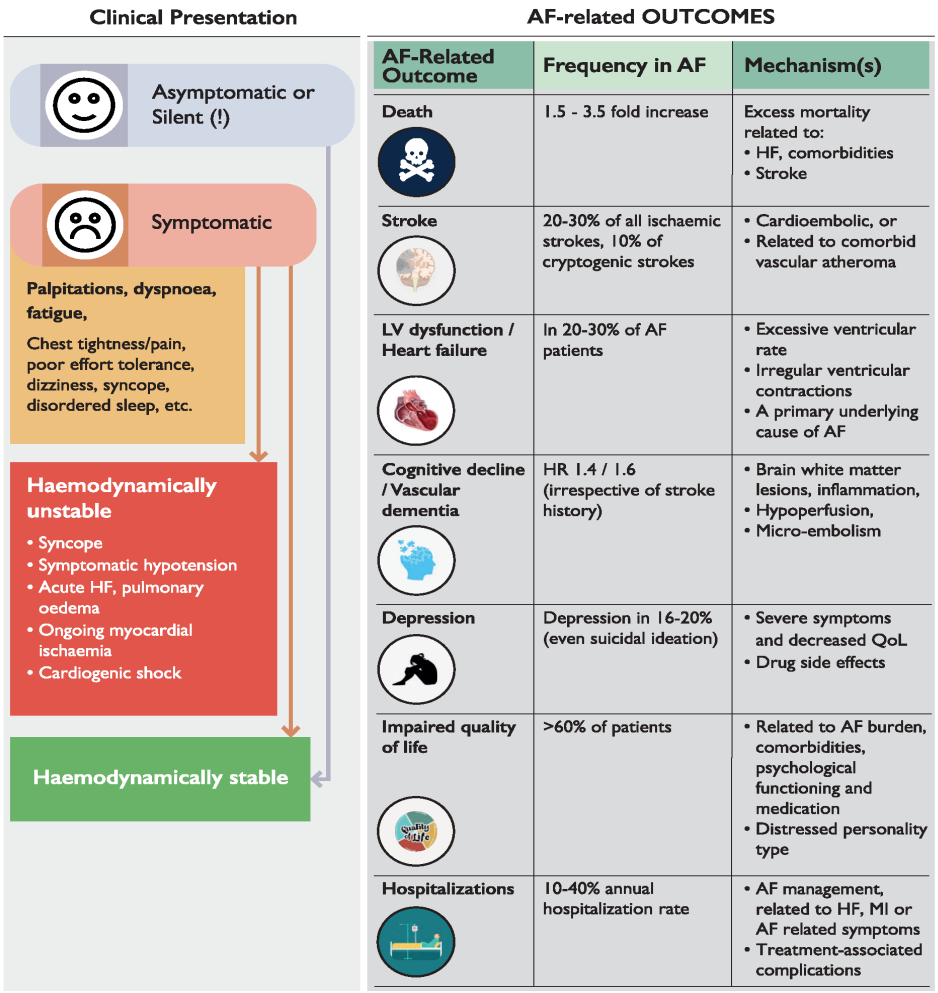

Figure 7. Clinical features of AF and AF-related outcomes. European Heart Journal 2020 Aug 29; ehaa612.doi:10.1093/eurheartj/ehaa612. Online ahead of print. Reprinted by permission of Oxford University Press

Symptoms are an important factor in both AF diagnosis and treatment and are often the reason patients seek medical attention (62). Palpitations are the most common symptom reported (63). The true prevalence of asymptomatic AF is, of course, unknown, but studies have found a range somewhere between 10-35% of patients with AF that are asymptomatic (63, 64). Regardless of symptoms the risk of AF-related mortality and morbidity is high (28). In patients with incidentally detected AF, the use of OAC has been shown to reduce mortality and morbidity (11). Most patients with AF are symptomatic, with as high as 16.5% having severe or disabling symptoms and a modified European Hearth Rhythm Association (EHRA) score 3-4 (see Table 3). This is strongly correlated with impaired quality of life in those patients (65). Both AF symptoms and quality of life were associated with a higher risk of hospitalisations (65). The modified EHRA symptom scale has been recommended to be used to guide symptom-oriented treatment options (66), shown in Table 3.

Modified EHRA score	Symptomst	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

Table 3. The modified EHRA score used for assessing if patients are functionally affected by their AF symptoms. Adapted from Wynn et al, The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification, Europace 2014;16(7): 965-72

2.6 SCREENING FOR ATRIAL FIBRILLATION

AF fulfills most of the WHO's criteria for population screening (15), see Table 4. Wilson and Jungner published their *Principles and practice of mass screening for disease* more than fifty years ago and this is still considered the gold standard for screening programs around the world. Wilson and Jungner proposed 10 principles that were to serve as a guide for planned screening.

Wilson and Jungners principles of screening
• The condition sought should be an important health problem
• The natural history of the condition, including development from latent to declared disease, should be adequately understood
• There should be a recognisable latent or early symptomatic stage
• There should be a suitable test or examination
• The test should be acceptable to the population
• There should be an agreed policy on whom to treat as patients
• There should be an accepted treatment for patients with recognised disease
• 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

Table 4. Wilson and Jungner's 10 principles that should be considered when making a screening decision. Adapted from Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. Boletin de la Oficina Sanitaria Panamericana Pan American Sanitary Bureau. 1968;65(4):281-393

Screening for AF and initiation of OAC therapy could potentially prevent stroke from AF in high-risk patients, but the optimal screening program and strategies are not yet defined. Studies with hard endpoints are awaited. ECG-screening is costly and therefore clinical risk-factors and risk scores such as the CHA_2DS_2-VASc score have been used to identify high-risk patients in screening studies, for example the STROKESTOP I study, where the screening resulted in a 30% increase in prevalence of AF in participants with CHA_2DS_2-VASc$\geq$ 2 (10).

The 2020 ESC AF guidelines recommend opportunistic screening for AF in individuals >65 years of age with a class I, evidence level B (8). This is mainly based on the dominance (better performance and cheaper) of opportunistic screening versus systematic screening in the SAFE study from 2005 (67). The opportunistic screening methods recommended by the guidelines is by pulse palpation or an ECG rhythm strip. They also give a class I recommendation for short term-ECG recording followed by continuous ECG monitoring for at least 72 hours in patients with transient ischaemic attack (TIA) or ischaemic stroke and regular interrogation of pacemakers and implantable cardioverter defibrillators (ICD) for atrial high-rate episodes

(AHRE), which are associated with an increased risk of overt AF (68).

Although both opportunistic and systematic screening are more effective in diagnosing AF than routine practice, the cost of systematic screening is higher, which influences the overall gain for society (69). The 2020 ESC AF guidelines give a class IIa, evidence level B indication (should be considered) for systematic screening for AF in individuals >75 years of age or those at high risk (8). Two Swedish trials on systematic screening for AF in 75-year-olds found 5.2% and 3% respectively of the screened individuals to have new AF (10, 70). The participants all had a CHA_2DS_2-VASc score ≥ 2 making them eligible for OAC treatment.

Finding the optimal screening population is an ongoing quest. A study using a computer simulation model based on the STROKESTOP I study and scientific literature found that the optimal screening age was 75 years with the lowest cost per quality adjusted life year (QALY) gained (71). Whether screening programs can reduce stroke and mortality remains an unanswered question. Several large randomised controlled AF screening studies are ongoing-including the STROKESTOP studies, SAFER, GUARD AF and LOOP studies-that will help answer that question (10, 72-75). One publication from 2018 presenting a five-year follow-up of participants in a systematic AF screening study in Sweden showed that stroke was indeed significantly reduced in the intervention area compared to the control area in a post-hoc population-based study (17). US Preventive Services Task Force (USPSTF) does not recommend screening for AF because it considers current evidence insufficient (76).

Whether or not screening for AF is cost-effective has also been studied. The results from the SAFE study (67) suggested opportunistic screening of men and women >65 years of age was cost-effective. A more recent study from the Netherlands where systematic screening was done in >65-year-olds at the same time as they were receiving seasonal influenza vaccination indicated that this would be cost-effective and could be implemented in primary care (77).

A meta-analysis (25 AF screening studies from 14 countries between 2002 and 2015) on the effectiveness of screening for AF found that active screening among individuals 40 years and older was effective and that the organisation of the screening seemed to be more important than the modalities used for rhythm detection (78).

Screening identifies new AF cases, but designing an ideal screening program is complex. For screening to be considered effective it has to combine: 1) choosing individuals that might benefit from screening, 2) using safe, convenient and easily applied screening tools for participants and personnel and 3) having a reliable, precise and validated screening modality at the right cost.

2.7 SCREENING MODALITIES

Methods for recording ECG have come a long way since Einthoven's second model was manufactured by Cambridge Scientific Instrument Company in the year 1911, see Figure 8a. Today's techniques allow ECG recording by easy wearables, see example in Figure 8b.

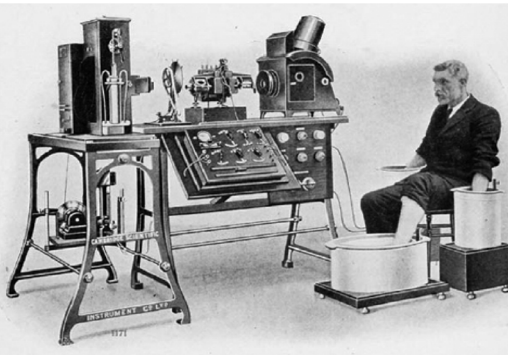

Figure 8a. Einthoven's second ECG model Reprinted by permission of Oxford University Press

Figure 8b. Wearable ECG reprinted by permission of Helge Brandberg

Over the last few years, heart rhythm detection technology has accelerated and numerous new methods of detecting AF have emerged, ranging from automated oscillometric blood pressure devices, photopletysmographic (PPG)-based smartphone applications to implantable leadless cardiac monitors (79). A summary of the most common methods is presented in the latest ESC AF Guidelines, see Figure 9 (8). When irregular pulse is detected by a screening tool, a 12-lead ECG or a rhythm strip of at least 30 seconds interpreted by a physician accustomed to analysing ECG rhythm is necessary for establishing an AF diagnosis (8). The methods can hence be divided into those requiring an ECG for confirmation and those that do not.

2.7.1 Methods needing ECG confirmation

Pulse palpation is unarguably the cheapest screening tool for AF. It has to be seen as a triage test because it needs to be followed by an ECG for confirmation of AF diagnosis, which again influences the actual costs of this screening method. A meta-analysis from 2016 by Taggar et al. in which pulse palpation was compared to blood pressure monitors (BPM), non-12-lead ECGs and smartphone applications found pulse palpation to have the lowest diagnostic accuracy of identifying AF with a sensitivity of 0.92 and specificity of 0.82 (80). When laymen were asked to palpate their radial pulse and then directly perform a 30-second single-lead ECG, the sensitivity was merely 25% per measurement occasion (20).

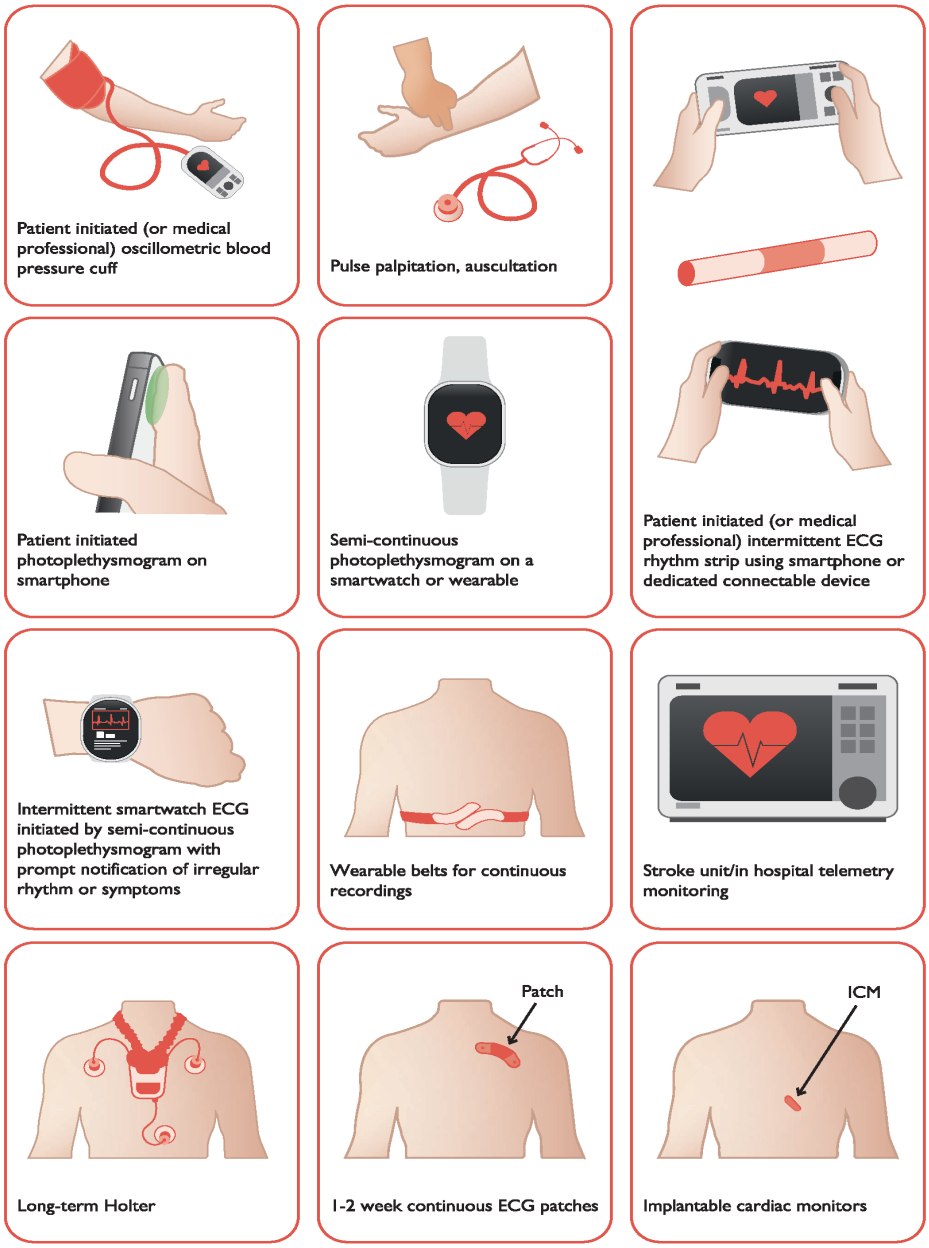

Figure 9. Systems used for AF screening. European Heart Journal 2020 Aug 29; ehaa612. doi:10.1093/eurheartj/ehaa612. Online ahead of print Reprinted by permission of Oxford University Press. Reprinted by permission of Oxford University Press

Blood pressure devices can also give an indication of irregular pulse. A study on automated oscillometric BPM Microlife WatchBP Home showed a reasonable sensitivity of 80.6% and a high negative predictive value of 99.8% (81). The same meta-analysis from Taggar et al. comparing pulse palpation to BPM found BPM from the six studies included to have sensitivity of 98% and a specificity of 92%, making it more accurate than pulse palpation (80).

Smartphone camera-and PPG-based application Cardio Rhythm had higher sensitivity (92.2%), similar specificity (97.7%), lower positive predictive value (53.1%) and similar negative predictive value (99.8%) for AF detection when compared to the single-lead ECG by AliveCor (82).

2.7.2 Methods not needing ECG confirmation

There are several ECG rhythm-recording methods available that do not need a 12-lead ECG registration for AF diagnosis. These vary in time range of heart rhythm assessment from intermittent to more continuous and from handheld or mobile devices to invasive monitoring devices.

2.7.2.1 Intermittent ECG recording devices

Atrial fibrillation, especially in patients with new onset, is usually paroxysmal and short in duration and as a result has often terminated by the time a stand¬ard electrocardiogram is acquired. To overcome this limi¬tation several types of ambulatory ECG recording devices have been developed. MyDiagnostick and the Zenicor ECG are one-lead handheld devices for intermittent ECG recordings that have been shown to be feasible methods for AF screening (10, 83), see Figure 10. The automatic algorithm used by the Zenicor device has been shown to be safe in AF screening, with sensitivity of 97.8% on ECG level, 100% sensitivity on individual level and a negative predictive value of 99.9%(84). AliveCor KardiaMobile is a smartphone-based device that records a single-lead ECG than was shown to be better in finding AF when performed twice weekly for a year when compared to routine care (85), see Figure 11.

Figure 10. Examples of intermittent handheld ECG devices. Reprinted by permission of a) Zenicor, b) Mydiagnostick and c) AliveCor KardiaMobile

2.7.2.2 Continuous ECG monitoring devices

There are many non-invasive continuous monitoring devices available. The traditional Holter monitors are widely used throughout the world, usually with monitoring time between 24-72 hours, using 3-7 ECG leads. A more recent evolution of continuous monitoring is the ECG patch, a cutaneous patch that continuously records a single-lead ECG for up to 14 days, see Figure 11. In a pilot study comparing the standard-care of 24-hour Holter monitoring to the Zio Patch, the Zio Patch identified 58% more new AF cases as a consequence of the extended ECG recording duration. The device was well tolerated by the participants (86). The Zio Patch along with two other modern continuous monitors, the Carnation Ambulatory monitor and the Nuubo vest, were compared to the traditional event-recorder Novacors R-test in participants with implanted pacemakers. All three were more accurate than the R-test (87). A simulation study recently published in which the Zio patch was used as a continuous ECG monitor, and 350,000 computer simulations estimated screening strategies involving intermittent ECG of any frequencies and duration up to14 days. The study found that an intermittent screening protocol of twice daily screenings for 14 days would have detected about 52% of individuals with AF in an asymptomatic population compared to continuous ECG monitoring. Increasing the screening protocol to four times daily would have identified 66% of the individuals with new AF (88). Such simulation studies can help in designing the optimal AF screening program.

Figure 11. Non-invasive continuous monitoring, the Zio patch. Reprinted by permission of Irhythm technologies

Invasive monitoring devices, so-called implantable loop recorders (ILR) or implantable cardiac monitors (ICM) are implanted subcutaneously to continuously monitor arrhythmias. The newer ones have AF algorithms and have been studied in cryptogenic stroke patients, one of those being the CRYSTAL-AF study which found 9% of the stroke patients with AF after 6 months in the ILR group compared to the 1% found in the routine care group (89). The ASSERT II trial used ICM to study to what extent subclinical AF was present in older people (>65 years) and found that subclinical AF > 5 minutes occurred at an incidence rate of 34.4% per person year (90). In the recently published LOOP study in which >70-year-olds with at least one additional risk factor according to the CHA_2DS_2-VASc score had an ILR implanted, the cumulated incidence at 3 years for AF >6 minutes was 33.8%.

The STROKESTOP study (NCT01593553), LOOP study (NCT02036450), STROKESTOP II study (NCT02743416), GUARD-AF (NCT04126486) and SAFER (ISRCTN16939438) study are all ongoing, randomised controlled studies, that will evaluate whether the applications of newer devices in selected clinical scenarios will improve clinical outcomes.

2.8 BIOMARKERS IN ATRIAL FIBRILLATION

Several plasma biomarkers have been proposed as possible aids in diagnosing AF and also in predicting AF related mortality and morbidity (91). Different biomarkers representing various pathophysiological pathways such as inflammation (IL-6, CRP), myocyte damage (troponin I and T), atrial dilatation or increased wall stress (natriuretic peptides) and altered haemodynamics (GFR, cystatin-C) have been studied, to name a few (91). Structural remodelling of the atria with fibrosis and connective tissue deposition (92) causes electrical dissociation between muscle bundles (93) and atrial conduction abnormalities which, in turn, become a substrate for AF. This structural remodelling can be caused by conditions such as hypertension, coronary artery disease and heart failure, among others (94), as well as atrial fibrillation itself (95) and is partially reversible when the underlying disease is treated (96).

N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) is a well-known marker for heart failure (97). It is excreted in response to dilatation and increased pressure and volume in the heart (98). NT-proBNP is also the best-studied biomarker in patients with AF and the most recognised one to predict incident AF, see Figure 12 (99, 100). It has also been shown to be associated with increased risk of stroke and mortality in AF patients (19) and it was included along with Troponin T in the ABC stroke risk score, which performed better than the most commonly used clinically based risk score (46).

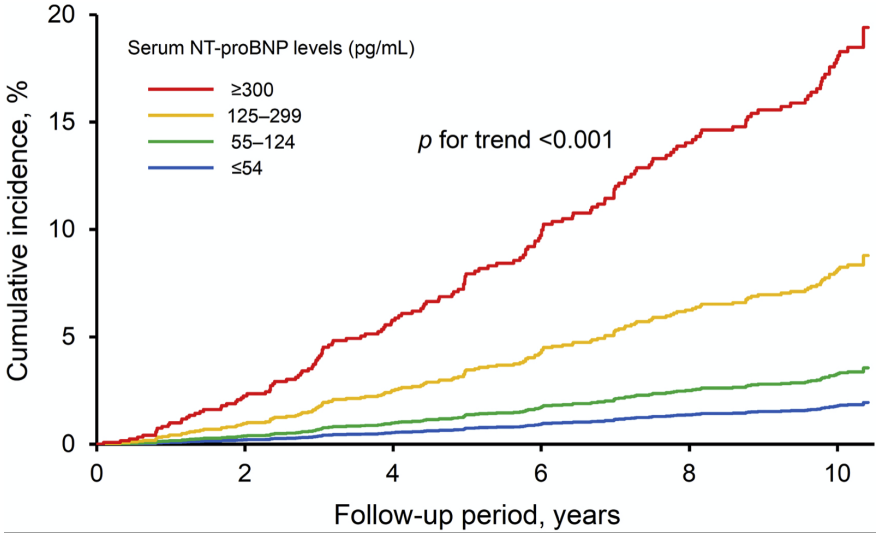

Figure 12. Nagata T et al. Serum N-terminal pro-B-type natriuretic peptide as a predictor for future development of atrial fibrillation in a general population: the Hisayama Study. International Journal of Cardiology. 2020. 10.1016/j.ijcard.2020.06.018. Published by permission of Elsevier

Clinical risk scores offer a modest predictive value of thromboembolic event with C-statistic that range from 0.549 to 0.638 (44). A subanalysis of the ENGAGE-AF-TIMI 48 trial showed that the biomarkers NT-proBNP, Troponin I and D-dimer, when added to the CHA_2DS_2-VASc score, improved the prognostic accuracy with a C-statistic increasing significantly from 0.586 to 0.708. After adjusting for CHA_2DS_2-VASc score, each biomarker had a remaining 2.8 to 4.2-fold increased risk for stroke, systemic embolic event or death (101).

A study using data-driven analysis of 40 cardiovascular biomarkers and clinical risk factors to fit a model for predicting AF found three biomarkers to be associated with AF: increased brain natriuretic peptide (BNP), increased fibroblast growth factor 23 (FGF-23) and a reduced TNF-related apoptosis-induced ligand-receptor 2 (TRAIL-R2)(102). Further studies on biomarkers are needed to find the optimal marker, which might differ for prediction of AF and outcomes such as stroke, death and/or major complications to OAC treatment. This could potentially form the basis of a more precise and personalised treatment.

2.9 SCREENING PARTICIPATION

The success of any screening program is dependent on the participation in the program. In a Swedish AF screening study the non-participants had significantly higher stroke risk (22). In the SAFE study, participants <75 years were more likely to

attend, but AF was more likely to be detected in those >75 years (67), showing that participation is lower for those at highest risk for both AF and its complications. In the STROKESTOP I study, socioeconomic factors such as education level, marital status, income level and immigrant background had significant impact on the participation. The distance to the screening centre also had an impact on participation, with higher participation for participants living closer to the screening centre (103). In the VIVA study, a Danish screening study for abdominal aortic aneurysm, peripheral arterial disease and hypertension, specially trained nurses operated mobile clinics which surely aided its screening uptake of 74.7% (104). Similarly, in a Norwegian study on the prevalence of AF and use of OAC treatment that offered home visits to disabled patients, participation was 82% (105). Even when the screening is part of a known and established screening program such as for breast cancer, screening uptake decreased with increasing socioeconomic deprivation and travel distance (106). How to best lower this socioeconomic gradient and to include in screenings those that require it the most is a complicated question likely with a multifaceted and non-homogenous answer.

3 AIMS

The main aim was to study different factors affecting the outcome of systematic population screening for atrial fibrillation in risk patients. These factors included the biomarker NT-proBNP, pulse palpation, socioeconomic, geographic and medical history disparities in participants and non-participants.

STUDY I

The aim was to study AF detection and predictors for new AF using NT-proBNP in a stepwise screening study in a high-risk population, as well as to study OAC treatment uptake and one-year adherence in those diagnosed with new AF.

STUDY II

The aim was to study detection of new AF using pulse palpation compared to one-lead ECG and to study if symptoms of palpitations were associated with the AF yield among participants.

STUDY III

The aim was to analyse geographic and sociodemographic disparities in the uptake of the STROKESTOP II study and compare the results between STROKESTOP I and STROKESTOP II after adding two new screening sites in STROKESTOP II.

STUDY IV

The aim was to study the potential yield of detected disease in non-participants and to compare characteristics of non-participants and participants in an atrial fibrillation study.

4 MATERIALS AND METHODS

4.1 STUDY POPULATION

All individuals born in 1940 and 1941 (n=28,712), residing in the Stockholm region were identified by Statistic Sweden using their 12-digit personal civic identification number, which is given to every permanent resident in Sweden upon birth or immigration for life-long use. After stratification for gender and age, a 1:1 randomisation provided an intervention group and a control group. The study population for studies I-IV was the intervention group (n=14 356) invited to participate in the STROKESTOP II, a population-based cohort study on AF screening. The control group underwent no intervention and were followed-up in registries. After controls of vital status, the intervention group was invited to screening by mail to whichever one of three AF screening clinics that was closest to their home residence. Participants were asked to self-report their medical history regarding prior AF diagnosis, OAC treatment, thromboembolic risk factors according to CHA_2DS_2-VASc score, pacemaker treatment, palpitation symptoms, weight and height. There were no inclusion criteria other than year of birth and home residence in the Stockholm region for those in the intervention group and no exclusion criteria. The intention-to-screen arm comprised 14,356 individuals, see Figure 13. Data for participants was collected between April 2016 and February 2018.

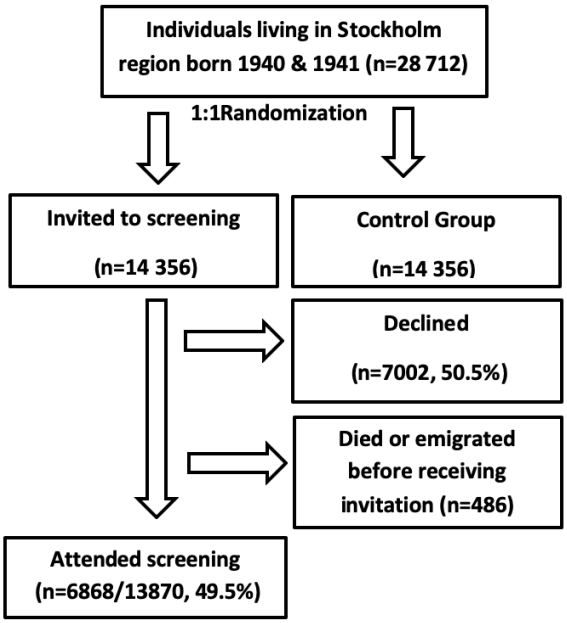

Figure 13. STROKESTOP II Study flow chart

4.2 STUDY I

Study I was a prospective cohort study on AF detection in 75-year-olds using NT-proBNP and intermittent single-lead ECG. At the screening sites, all participants without previous AF had NT-proBNP analysed from venous blood samples using point-of-care analysis (Cobas h 232, Roche diagnostics, Rotkreutz, Switzerland) (107). Participants were stratified into two groups based on their NT-proBNP result. Participants were in the low-risk group if NT-proBNP <125 ng/L and in the high-risk group if NT-proBNP ≥125 ng/L. These cut-off values had been defined based on a sub-study to the STROKESTOP I study (108) to select the individuals with highest risk for AF. All participants without previous AF recorded an index single-lead ECG consisting of a 30-second rhythm strip using the handheld Zenicor ECG device (Zenicor Medical Systems, Stockholm, Sweden). Individuals in the high-risk group continued with prolonged ECG screening using the Zenicor ECG device four times daily-at morning, noon, afternoon and evening-for two weeks. Individuals in the low-risk group underwent no further ECG investigation if their index ECG revealed sinus rhythm.

No ECG or further examination was performed in participants with previously known AF but if they did not have OAC treatment they were referred to cardiologist for assessment, as all participants received two points on the CHA_2DS_2-VASc scale based on their age alone. Participants with NT-proBNP ≥900 ng/L and no previous diagnosis of heart failure were referred to a cardiologist for echocardiography and assessment in addition to the ECG screening. In case of new AF diagnosis during the screening procedure, participants were referred to a cardiologist for a standard follow-up during which OAC treatment was initiated unless contraindicated. Blood pressure (BP) was measured in all participants and if it was >140/90 and no known diagnosis of hypertension, they were referred for further control to their general practitioner or a cardiologist.

4.2.1 Outcome measures

Atrial fibrillation was defined as a completely irregular rhythm with no organised or regular atrial activity of 30 seconds duration on single-lead ECG. Participants with AF diagnosed using handheld ECG did not undergo any additional ECG investigation. Initiation of OAC treatment was defined as an issued OAC prescription after a cardiologist visit and adherence to treatment at one-year follow-up.

4.2.2 Diagnostic modalities

The Zenicor ECG device, see Figure 14, records a 30-second ECG in lead I and

automatically transmits the encrypted recording to a password protected database. The Zenicor ECG device has been extensively validated and used in several previous AF screening studies (10, 109).

A validated computerised algorithm was used to identify ECG recordings with sinus rhythm or minor artefacts (84). These recordings were not systematically manually interpreted, but a random sample was inspected by cardiologists throughout the inclusion period. All ECGs identified by the algorithm as abnormal were manually interpreted by arrhythmia trained nurses and subsequently, all pathological ECGs were scrutinised by the study team cardiologists. Participants with insufficient signal quality (less than 50% of recordings interpretable) on handheld ECG or possible positive finding like atrial flutter (which can be difficult to interpret on a single-lead ECG) were offered a 5-day Holter recording. The medical records of participants with pacemaker treatment were studied for atrial high-rate episodes with a duration of at least six minutes and available device electrograms.

Figure 14. Handheld single-lead ECG – Image courtesy of Zenicor

4.2.3 Statistics

Baseline characteristics including age, sex, height, weight and previous medical history according to CHA_2DS_2-VASc were summarised using frequencies for categorical variables and means with standard deviation (SD) for continuous variables. For CHA_2DS_2-VASc and NT-proBNP both mean (SD) and median with 25th and 75th centiles were calculated. The following tests were used for differences among groups: The Chi2 test was used for categorical variables; students T-test was used for height and weight; and Mann-Whitney U test was used for CHA_2DS_2-VASc and NT-proBNP, which showed a skewed distribution. The relations between clinical variables and logarithmically transformed NT-proBNP with new AF were investigated in the group with NT-proBNP≥125 ng/L using multivariable logistic regression. A probability value of < 0.05 was regarded as significant. Analyses were per-

formed using STATA/MP 15.1 (StataCorp, 4905 Lakeway Drive College Station, TX77845, USA).

4.3 STUDY II

Study II was a diagnostic accuracy study that compared the yield of AF detection between pulse palpation and single-lead ECG.

4.3.1 Outcome measures

Irregular pulse was considered to be a positive test and recorded as such in the eCRF form.

AF was defined as irregular rhythm with no organised or regular atrial activity for 30 seconds on single-lead ECG or on a 12-lead ECG.

History of palpitations were noted in the eCRF as a binary yes/no variable to the question "Do you have palpitations?".

4.3.2 Diagnostic modalities

Trained healthcare professionals performed pulse palpation of the radial pulse for 30 sec in all participants in the STROKESTOP II study without previously known AF, see Figure 15. Regular pulse was defined as regular in rhythm and force. The pattern of irregularity was not especially defined. Directly following the pulse palpation, a 30-sec handheld single-lead ECG recording with the Zenicor ECG device was obtained and evaluated by the same health care professionals.

The ECG analysis with Zenicor ECG device used a computerised algorithm marking all ECGs with sinus rhythm as normal. ECGs with minor artefacts, poor signal quality or possible AF or another arrhythmia were flagged by the algorithm as abnormal. The algorithm has been extensively validated, showing a 100% sensitivity of the system in identifying AF on an individual level and a negative predictive value of 99.99 % (84). If the algorithm classified a recording as sinus rhythm and this was agreed upon by the study nurse, a 12-lead ECG was not deemed necessary. If the algorithm indicated AF, artefacts or if the signal quality was too poor for interpretation, a 12-lead ECG was obtained, and one of the cardiologists from the study team was contacted for interpretation.

The results from the single-lead ECG (and/or 12-lead ECG when deemed necessary) was used as reference standard in accordance to recent guidelines for AF diagnosis (8). Post hoc, all index single-lead ECGs were scrutinised by three cardiologists to confirm whether sinus rhythm could be clearly identified or whether a 12-lead ECG should have been taken at the time. A sensitivity analysis was per-

formed including participants from whom a 12-lead ECG had not been obtained and results from two weeks of intermittent single-lead screening following the index visit were imputed as a result. Participants that had not concluded the additional 2 weeks of screening were excluded from the sensitivity analysis.

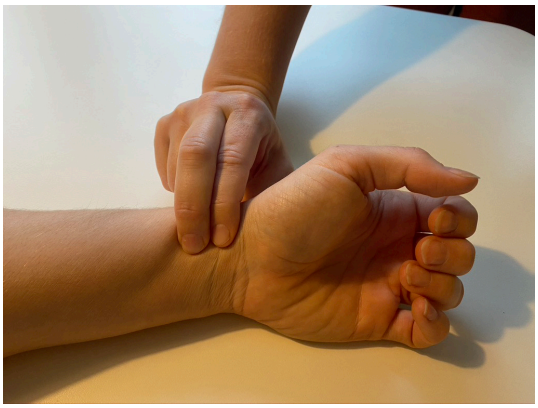

Figure 15. A demonstration of the radial pulse palpation

Participants were asked to answer the yes/no question "Do you have palpitations?" in a questionnaire before the visit. There was no request for a specification of character, duration or temporal context of palpitation symptoms.

4.3.3 Statistics

Based on previous studies on pulse palpation, for reliable sensitivity and specificity, we needed at least 4,984 participants to achieve 80 % power to show significant difference between the two screening tests (80).

Categorical variables were expressed as numbers and percentages. The demographics of individuals with and without new AF were compared using the Pearson's chi-squared test for categorical variables.

Diagnostic accuracy parameters of the screening test were derived from a 2x2 contingency table. We reported the number of true positives, true negatives, false positives and false negatives. We calculated sensitivity and specificity, accuracy, positive and negative predictive values, likelihood ratios as well as the post-test predictive values. Diagnostic accuracy parameters were expressed as means with 95% confidence intervals. We conducted subgroup analyses on the accuracy of the screening test for symptomatic vs. asymptomatic participants and compared their area under the curve.

McNemar's test for dependent proportions was used to test whether the pulse palpation test was equivalent to the handheld-ECG test. For all statistical comparisons,

a p-value < 0.05 was considered significant.

We reported the results of this study according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) statement. All analyses were performed using STATA/MP 15.1(StataCorp, 4905 Lakeway Drive College Station, TX77845, USA).

4.4 STUDY III

Study III was a cross-sectional prevalence study on the socio-demographics in the cohorts from the STROKESTOP I and II studies. The STROKESTOP I study, also a population-based cohort study on 75/76-year-olds in the Stockholm and Halland regions, is the first of the STROKESTOP studies (10). In the STROKESTOP I study socio-demographic differences of the participants were studied and lower education level, lower income level and immigrant status were all associated with lower participation (103). These findings were taken into consideration when designing the STROKESTOP II study to try to counteract the socioeconomic gradient. Two new screening sites were added-the Sodertalje Hospital site and Karolinska University Hospital Huddinge site-which were located closer to low-income neighbourhoods with a very low participation rate in the STROKESTOP I study, see Figure 16. In addition, a website (www.strokestop2.se) was launched for general information on AF, the study procedure and the study team. The patient information was translated to the nine most common languages in Sweden.

Figure 16. The site used in both STROKESTOP studies (pink pin) and the two new sites (blue and green pins) in the STROKESTOP II study

4.4.1 Data

The STROKESTOP II database comprises information on each invited person's residential parish (99 parishes in Stockholm). Statistics Sweden provided anonymised individual data for both participants and non-participants for each of the following socioeconomic variables: educational level, disposable income, immigrant and marital status. Invited persons who were not possible to classify based on the information in the national registers were grouped into an "other/unknown" category of the variable at issue. The same socio-demographic variables were considered and obtained in the STROKESTOP I study, but individual-level data was not obtained on the socio-demographic characteristics. Rather, the data used in STROKESTOP I were aggregated at the parish-level.

4.4.2 Statistics

P-values for the null hypothesis of equal participation in men and women and for each socioeconomic variable were obtained by Chi-square test. All tests were two-sided, and a value of $p<0.05$ was regarded as significant.

Geo-maps of Stockholm county displaying spatially smoothed participation ratios were estimated by hierarchical Bayes methods. A parish-specific participation ratio (PR) was based on the observed-to-expected participation, where the expected number of participants was obtained from the sex-specific rates for the total study population of the county. Spatially smoothed participation rates were obtained by running the hierarchical Bayesian mapping model (the Besag-York-Mollié model) implemented in the Rapid Inquiry Facility program(110). This procedure allows parish-specific participation rates to be smoothed towards global and local mean participation rate levels across the county, yielding "shrinkage" of the conventional observed to expected ratios—in line with principles for multi-level modeling(111). The corresponding statistical certainty geo-maps were obtained by calculating the posterior probabilities of a PR >1 given the data, denoted Pr (PR>1|data), using the Bayesian approach. A parish with data yielding strong statistical evidence of elevated participation, more precisely Pr (PR >1|data)> 0.90, was coloured green in the certainty geo-map. By contrast, a parish with lowered participation rate, Pr (PR< 1|data)> 0.90, was coloured red. The remaining parishes were coloured yellow. The choice of 0.90 for identifying an area with elevated/lowered participation rate has been shown to provide a cut-off with reasonable sensitivity and high specificity (112).

Binary logistic regression was used for the univariate and multivariable analyses of socio-demographic factors for the outcome reflecting participation or

non-participation.

The statistical computations were performed by using IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. For the spatial analyses, the Rapid Inquiry Facility free software (RIF 3.12).

4.5 STUDY IV

Study IV is an analytical cross-sectional study. The study population was the intention-to-screen group invited to participate in the STROKESTOP II study.

4.5.1 Data variables

Disease histories of the individuals were identified using data from the National Patient Register (NPR) (113). Disease history variables were collected from inpatient (hospitalisations) and outpatient (a visit to the hospital, clinic or associated facility for diagnosis and treatment) records from January 1st, 2001 up to the index date. Thirty-one disease variables were chosen based on clinical experience. Medical conditions were classified as present if the subject had at least one inpatient or outpatient record during this period. Possibly curable conditions were limited to shorter time periods (e.g., cancer was defined as prevalent only if a record occurred within 3 years proceeding index date). The disease history variables (and ICD-10 codes)

Disease	ICD-10 Codes and procedure codes beginning with
Atrial fibrillation	I48
OAC treated atrial fibrillation	I48 & ATC Codes beginning with B01
Ischemic stroke	I63, I639
Pulmonary embolism	(Inpatient only) I26, Z867A
Thromboembolism	I63, I64, I693, I694, G45, I74
Intracerebral bleeding	I61, I691
Other intracranial bleeding	I60, I62, S064, S065, S066, I690, I692
Hospitalization due to bleeding	(Inpatient only) I60, I61, I62, S064, S065, S066, I690, I691, I692, I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922, N02, R319, N950, N939, N501A, H113, H313, H356, H431, H450, H922, I312, J942, M250, R04, R58, D500, D629, T810, Z513
Anaemia	D5, D60, D61, D62, D63, D64
Myocardial infarction	I21, I22, I252
Vascular disease	I21, I22, I252, I170, I171, I172, I173
Peripheral artery disease	I70, I71, I72, I73
Heart failure	I50, I110, I130, I132, I255, K761, I42, I43
Mitral stenosis	I342, I050, I052, Q232

Mechanical prosthetic valve	Z952
Pacemaker	Z950, Z450
Hypertension	I10, I11, I12, I13, I14, I15
Hyperlipidemia	E78
Diabetes	E10, E11, E12, E13, E14
Liver disease	K70, K71, K72, K73, K74, K75, K76, K77
Chronic kidney disease	N18, N19
Hypothyroidism	E00, E01, E02, E03, E890
Thyrotoxicosis	E05 during previous year before index
Chronic obstructive pulmonary disease	J43, J44
Rheumatoid arthritis	M05, M06
Osteoarthritis	M15, M16, M17, M18, M19
Alcohol index	E224, F10, G312, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90, Y91, Z502, Z714
Dementia	F00, F01, F02, F03, F051, G300, G301, G308, G309
Cancer (last 3 years)	C0, C1, C2, C3, C40, C41, C42, C43, C45, C46, C47, C48, C49, C5, C6, C7, C8, C9
Parkinson's disease (%)	G20, G21, G22, G23, G24, G25, G26
Psychiatric diseases (%)	F2, F3, F6

Table 5. Data variables and their ICD-10 codes included in the dataset.

included in the dataset are shown in Table 5.The Swedish prescribed drug registry The Swedish prescribed drug registry (114) was used for data on prescription medicine dispensings for participants and non-participants. Based on clinical experience 13 prescription medicine classes were included in the analysis, see Table 6. Active treatment was defined by at least two dispensings of the medicine within 3 years

Prescription medications	Anatomical Therapeutic Chemical (ATC)-Codes beginning with
Anticoagulant	B01
Psychiatric medications	N06
Neuroleptics	N05A
Parkinson's disease medications	N04
COPD medication	R03
Diabetes medications and insulin	A10
Antihypertensives	C02
Diuretics	C03
Beta blockers	C07
Calcium antagonists	C08
RAAS inhibitors	C09
Lipid lowering agents	C10

Table 6. Medical prescription categories included in the dataset.

preceding index date.
Individuals were classified according to the weighted Charlson's comorbidity index (quantifies the burden of disease and corresponding 1-year individual mortality) (115). CHA_2DS_2-VASc scores were estimated from ICD-10 codes. Multimorbid individuals were classified according to the criteria used by the Swedish National Board of Health and Welfare (116). For individuals to be considered multimorbid they had to fit at least one of the following criteria in the 12-month period prior to index date:

- They had to have been hospitalised at least 3 times with a main diagnosis from separate ICD-10 chapters.
- They had to have been hospitalised at least 20 days.
- They had to have been hospitalised at least 4 times.
- They had to have had at least 8 outpatient visits.

Statistics Sweden provided anonymised individual data for both participants and non-participants for the following socioeconomic variables: educational level based on school level completed (primary, secondary, tertiary), disposable income (low, medium, high), immigrant (born in Sweden, born abroad) and marital status (unmarried, married, divorced, widow/widower).

4.5.2 Index dates

Individuals in the intention-to-screen group received up to three invitations to attend the screening study. Among participants, the average delay from the last received call to their examination was 16 days (SD: 9, Range: 0 to 386). The date of the examination was used as the index date for participants, but index dates were not available for non-participants. To handle this issue, randomly sampled numbers from the empirical distribution of time delays among the participants were used to assign hypothetical examination dates to the non-participants. This made it possible to relate disease histories and pharmaceutical dispensation patterns to specific periods prior to examination uniformly for all individuals in the dataset.

4.5.3 Statistical analysis: predicting participation

A random forest was trained to predict the propensity score for participation. Random forests are strong alternatives to parametric models (e.g., logistic regression) in the presence of non-linear effects and unforeseen interactions between covariates, as they do not require these to be specified in advance. In addition, they can flexibly handle data with many covariates. Specifically, the regression forest algorithm

introduced by Athey et al. (117) was applied using the grf package for R (118). All variables available for both participants and non-participants were included as predictors. Fifty thousand regression trees were grown and parameters that control the complexity of the model were tuned (e.g., the minimum number of individuals allowed in each group in the regression trees) using the cross-validation feature implemented in grf.

4.5.4 Generalization weights: potential screening yield

Out-of-bag predictions from the forest were used to construct inverse probability of sampling weights (IPSW) for each participant (119, 120). These weights were used to estimate potential screening yield of disease under a hypothetical scenario in which everyone participated. In addition, another set of weights was defined to estimate screening yield of disease for non-participants. The potential screening yield was measured as estimated proportions of

- Prior AF
- Unmedicated AF (defined as prior AF and no OAC treatment)
- New AF (screening detected AF)
- Untreated AF (defined as the sum of new AF and unmedicated prior AF)
- Participants' CHA_2DS_2-VASc scores as a proxy for patients with high risk for stroke if detected with new AF and therefore would probably benefit from screening

When applicable, p-values were estimated with Chi2 test for binary variables (n, %), with t-test for continuous variables (mean, SD). Covariate balance checks for inverse probability weighting methods were done by plotting standardised differences for means and proportions for all covariates, shown in Figures 17 and 18. The weights were able to improve covariate balance for both target populations; the average absolute standardised difference taken over all covariates before and after weighting was 0.124 versus 0.06 (52% imbalance reduction) and 0.068 versus 0.035 (48% imbalance reduction) for the non-participants and intention-to-screen population, respectively.

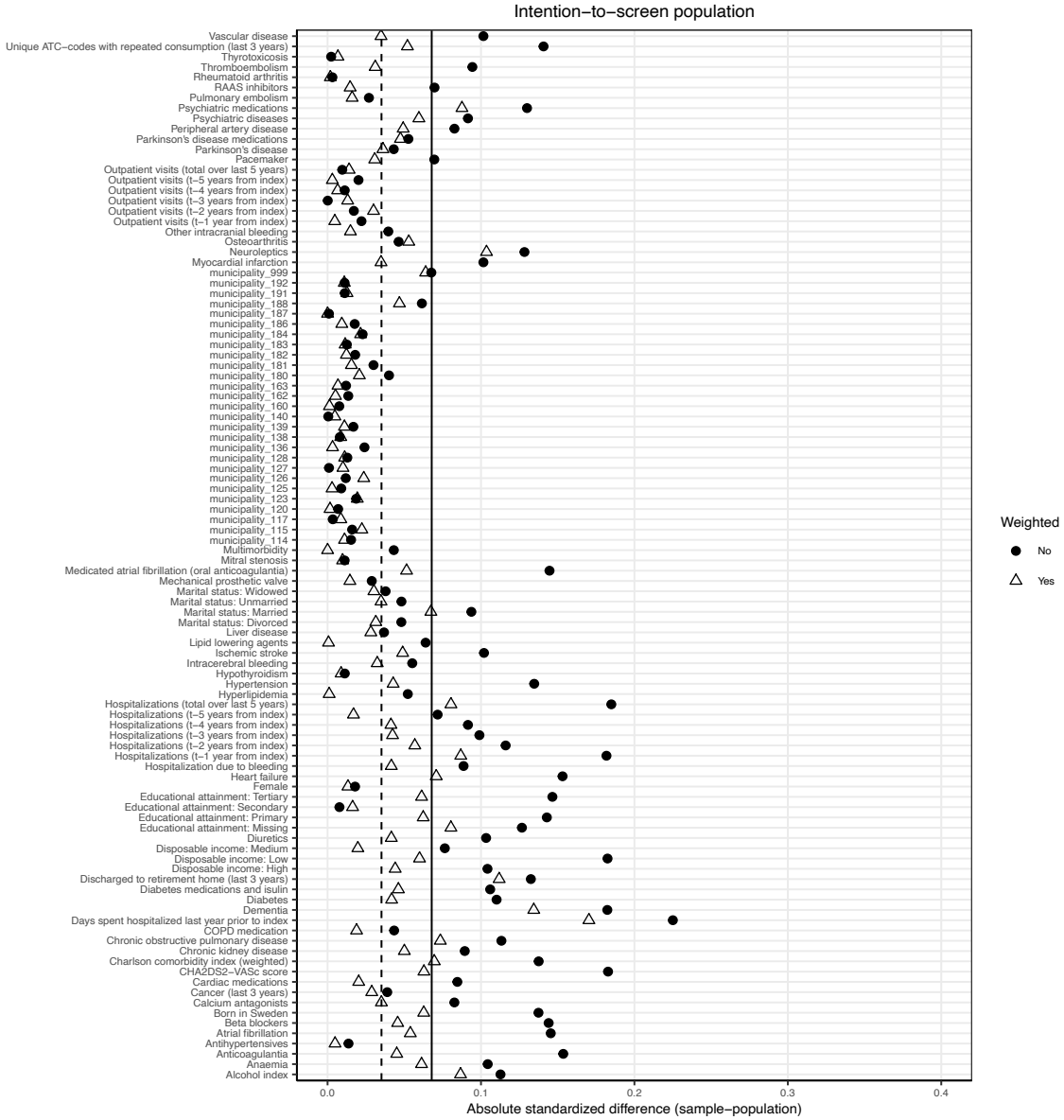

Figure 17. Covariate balance in the intention-to-screen group

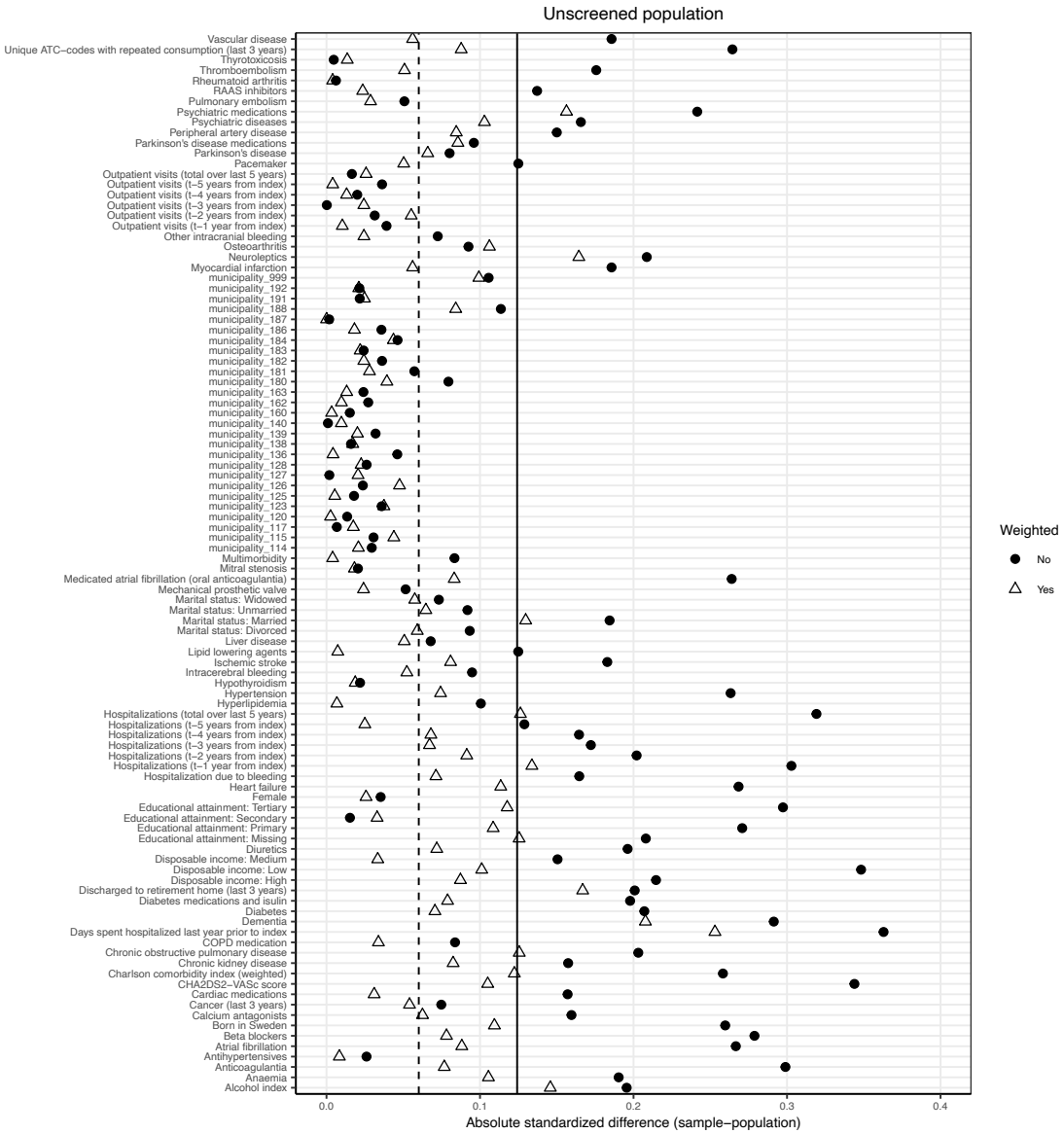

Figure 18. Covariate balance in the non-participants group

Inverse probability weighting requires overlap in the covariate distributions between participants and non-participants, also known as positivity (121). Two checks were performed to assess potential violations of the positivity assumption (i.e., whether or not there are values of the covariates at which there are no participants or non-participants). Firstly, histograms of the distribution of estimated propensity scores by participation status were compared (Figure 19), which did not show any areas of non-overlap (implying that non-positivity was not an issue) (122). Secondly, we checked that stabilized versions of the weights have mean close to one (non-participants: [mean: 1.07; SD: 0.67; min: 0.31; max: 7.78]; intention-to-screen: [mean: 0.95; SD: 0.29; min: 0.62; max: 3.82]), as suggested by Austin & Stuart (121).

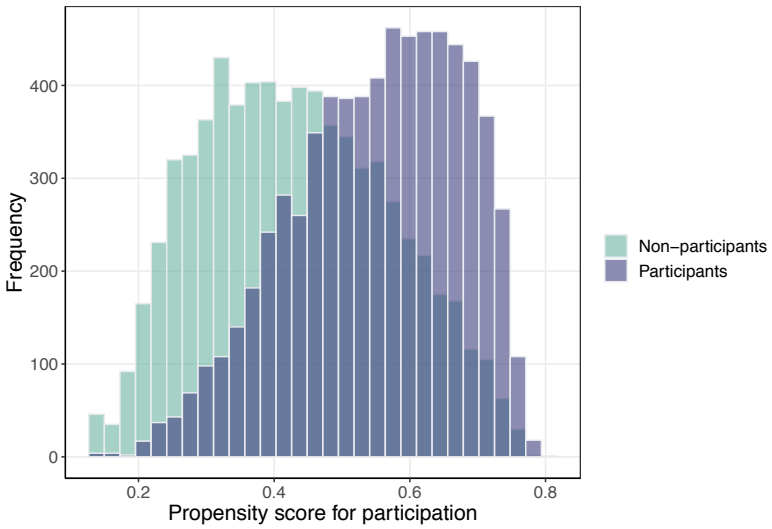

Figure 19. Histograms of the distribution of estimated propensity scores by participation status

5 ETHICAL CONSIDERATIONS

All the research projects depended on human participants. The studies complied with the Declaration of Helsinki, and the protocol was approved by the regional ethics committee in Stockholm (DNR 2015/2079–31/1). All participants received oral and written information and signed informed consent documents.

To screen for a disease in individuals free from symptoms can be controversial when the treatment offered entails risks, as oral anticoagulation treatment does. The potential benefits of preventing stroke appear great, as the costs for stroke are high and causes severe suffering for patients. Therefore, it is important to be able to perform randomised controlled trials to answer the question if screening does indeed benefit patients as well as society.

The STROKESTOP studies are ongoing prospective trials with the aim of studying whether or not treating screening-detected AF can prevent stroke and death. Our participants were all at least 75 years of age and as such were considered to have an increased risk of stroke according to the CHA_2DS_2-VASc score even without any other co-morbidities. AF discovered by any other mean would most probably lead to a recommendation of OAC treatment. A very recent study found that individuals with screening detected AF had significantly higher mortality risk than the individuals without AF (16) and observational data suggest that screening-detected AF responds in the same way as AF discovered by routine care, thus favouring screening (11). All participants with a new AF were referred to a dedicated cardiologist for assessment before initiation of OAC treatment in accordance to guidelines.

As in any screening program, the individuals participating might have worried about their results, both positive or negative, or may have felt falsely assured by a negative result. This is something that all screening studies have to acknowledge. In this case, the possibility to answer the question ‘whether screening can prevent stroke and death’ was considered to be of more importance.

Participation in the studies entailed that the patients submitted blood samples, which could have caused some discomfort. Blood pressure was measured, but that was considered non-harmful to the participants. The single-lead ECG method was non-invasive and did not physically harm the participants, but the high-risk group had to record intermittently for two weeks, which could have been of some disturbance to their everyday life and routines.

Any participant with an abnormally high NT-proBNP and no previous history of heart failure was referred to a cardiologist for echocardiography control and assessment. All participants with abnormally high blood pressure without previous his-

tory of hypertension were referred to their general practitioner. All participants with severe arrhythmia were followed up by a cardiologist as were all participants with new AF.

Studies III and IV were partly register based. We used information from the National Patient registry, the Swedish prescribed drug register and Statistics Sweden provided socioeconomic data. In these national data bases individuals are not given the option to opt-out of registration so there is a substantial amount of sensitive data. As the registry sets contain sensitive data, Sweden's national authorities de-identify all data before giving it to researchers. The key to connect the data to participants is kept at the Social Board of Health and Welfare for safe keeping. The risk of violating individual patients' integrity within the context of these large sets of anonymised data generating aggregated results was considered to be very low.

For the participants the privacy violation was considered exiguous as sensitive personal data was collected first after the informed consent was given. The participants were invited via mail, where it was stated clearly that participation was non-compulsory, and the possibility to withdraw was available. All personal data is stored in a safe database provided by Zenicor, and original files are stored according to Swedish research data storage recommendations.

6 RESULTS PER STUDY

6.1 STUDY I

The number of individuals that accepted the invitation to participate in the STROKESTOP II study was 6,868 or 49.5% of the intention-to-screen group. Previous AF was found in 553 (8.1%) participants, out of which 90.2% were on OAC treatment. Participants with known AF not on OAC treatment were referred to a cardiologist for assessment.

NT-proBNP was analysed in 6,315 participants. Values ≥125 ng/L were found in 3,766 (59.6%) of the participants, classing them according to our definition as "high-risk" for atrial fibrillation. These individuals were invited to participate in prolonged screening using single-lead ECGs intermittently for two weeks.

6.1.1 AF detection and prediction

All participants performed an index single-lead ECG at the screening visit. In 29 participants a new diagnosis of AF was made on the index-ECG. All participants save one belonged to the high-risk group. The high-risk group performed prolonged screening, and in additional 136 individuals were diagnosed with new AF during the two weeks of screening. In total, 165 new cases of AF were detected. In the high-risk group, the detection rate was 164/3,766 (4.4%, 95% CI 3.7-5.1), see Figure 20. In the entire group attending screening, new AF was detected in 165/6,315 (2.6%, 95% CI 2.2-3.0) of participants without previously known AF. The screening procedure resulted in an almost 30% increase in AF prevalence among participants in total, or an absolute increase in AF prevalence from 8.1% to 10.5%. The number of people who needed to be screened in this population to find one new case of AF was 38.

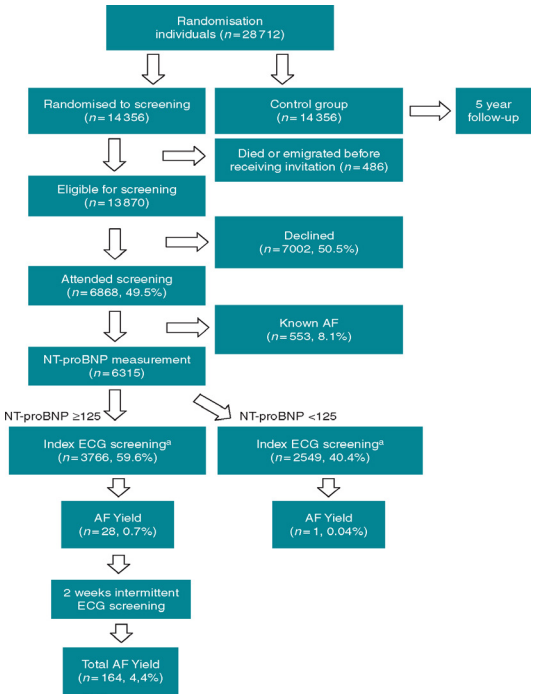

Figure 20. Study flow chart and AF yield in the high-risk group. EP Europace 2020;22(1): 24-32. Reprinted by permission of Oxford University Press

The 29 participants diagnosed with new AF on their index-ECG had significantly higher NT-proBNP than those diagnosed with new AF during the following two weeks, with a median NT-proBNP levels of 1,308 ng/L (IQR 663-2,180 ng/L) versus 305 ng/L (IQR 199-522 ng/L), see Figure 21.

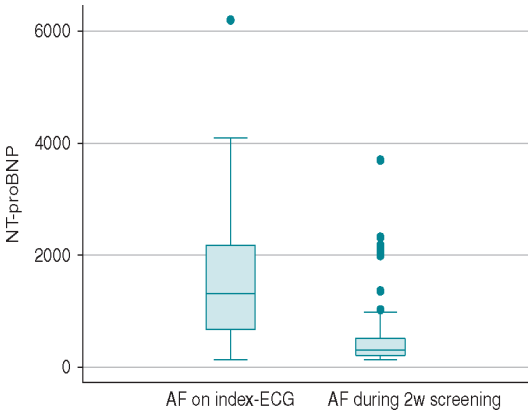

Figure 21. NT-proBNP levels in participants with new AF on index-ECG vs. 2weeks screening. EP Europace 2020;22(1): 24-32. Reprinted by permission of Oxford University Press.

The distribution of new AF stratified to NT-proBNP levels and CHA_2DS_2-VASc scores is depicted in Figure 22. The interquartile odds ratio from NT-proBNP quartile 1 to 4 was 4.19 (95%CI 2.54 - 6.93).

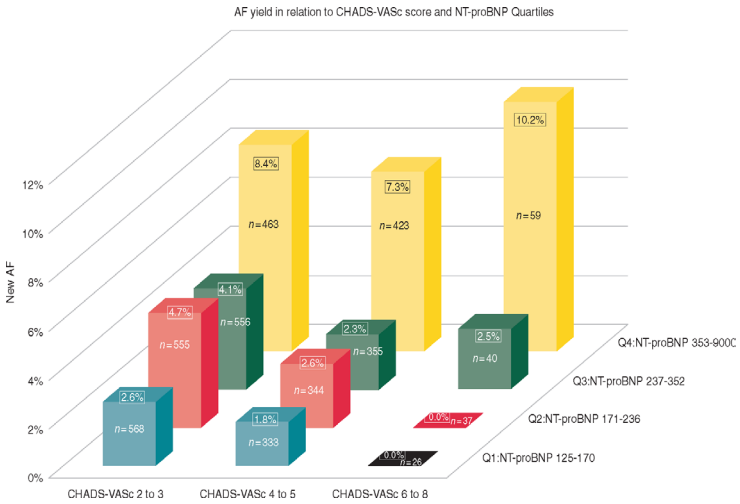

Figure 22. AF yield in relation to CHA_2DS_2-VASc score and NT-proBNP quartiles. EP Europace 2020;22(1): 24-32. Reprinted by permission of Oxford University Press.

NT-proBNP was the strongest predictor in the high-risk group for new AF, see Table 7.

Variables	OR (95% CI)	P-value
Congestive heart failure (yes)	0.85 (0.31-2.33)	
Hypertension (yes)	0.97 (0.70-1.36)	
Diabetes mellitus (yes)	0.65 (0.37-1.15)	
Prior stroke/TIA (yes)	0.83 (0.59-1.16)	
Vascular disease (yes)	0.52 (0.27-0.99)	0.047
Gender (female)	0.53 (0.38-0.74)	<0.001
BMI (kg/m^2)	1.05 (1.01-1.10)	0.011
Log NT-proBNP	3.06 (2.39-3.75)	<0.001

Table 7. Multivariable analysis for AF detection in the high-risk group. EP Europace 2020;22(1): 24-32. Reprinted by permission of Oxford University Press.

6.1.2 Use and initiation of oral anticoagulants

Of the 165 participants with new AF, 94.5% were initiated on OAC treatment after cardiologist assessment. Of those with previously known AF, a majority (90.2%) were on OAC treatment. Participants with previously known AF but not on OAC treatment were referred to a cardiologist for assessment. Not all of them accepted the referral but of those that did accept, 70.5% were initiated on OAC treatment. At one-year follow-up, 96% of the patients initiated on OAC treatment were still adherent to the treatment. In total 219/6,868 (3.2%) participants were diagnosed with new or previously untreated AF, thus making them eligible for OAC therapy.

None of the patients were referred for electrical cardioversion nor ablation at their initial cardiologist assessment. Pacemaker was implanted in four patients due to high degree AV-block on prolonged holter recording, and two were referred for left atrial appendage occlusion because of OAC contraindication. Of the participants with NT-proBNP >900ng/L that were referred to a cardiologist, two received a pacemaker, one was planned for coronary angiography and three of the participants were planned for aortic valve replacement. Thus, eight participants (0.2%) underwent invasive downstream therapy due to participation in the screening.

6.2 STUDY II

In total, 6,868 participants were included in the STROKESTOP II study. Previously known AF was found in 553 (8.1%) of the participants and those were excluded from analysis leaving 6,315 participants. Out of these 19 (0.3%) participants had no pulse palpation performed and in 137 (2.2%) participants the single-lead ECG was considered to be of insufficient signal quality with no 12-lead ECG obtained. These were excluded, leaving 6,159 participants included in data analysis, see Figure 23.

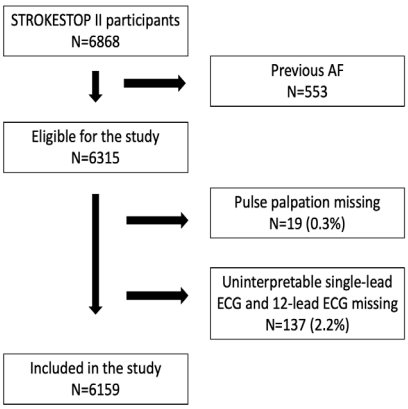

Figure 23. The study flow chart

Baseline characteristics of participants with regular and irregular pulse are shown in Table 8. Female sex, congestive heart failure, hypertension and history of palpitations were significantly more frequent in participants with irregular pulse.

Included participants	Regular pulse (n=5698)	Irregular pulse (n=461)	p-value
Congestive heart failure n (%)	62 (1.1%)	11 (2.4%)	0.013
Hypertension n (%)	2,880 (50.5%)	259 (56.2%)	0.020
Diabetes mellitus n (%)	614 (10.8%)	48 (10.4%)	0.808
Stroke/TIA/thrombo-embolism n (%)	401 (7.1%)	39 (8.5%)	0.254
Vascular disease n (%)	349 (6.1%)	33 (7.2%)	0.376
Female n (%)	3,220 (56.5%)	215 (46.6%)	<0.001
History of palpitations n (%)	1,664 (29.2%)	163 (35.4%)	0.005

Table 8. Baseline characteristics of participants with regular versus irregular pulse

6.2.1 AF screening accuracy of pulse palpation

Irregular pulse was found in 461 out of 6,159 (7.5%) participants. AF was diagnosed in 22 of those with irregular pulse (4.8%). The largest part of the participants had regular pulse (n=5,689) and of those, six were diagnosed with AF during the visit (0.1%). In total AF was diagnosed in a total of 28 participants at the single-time-point visit, see Figure 24.

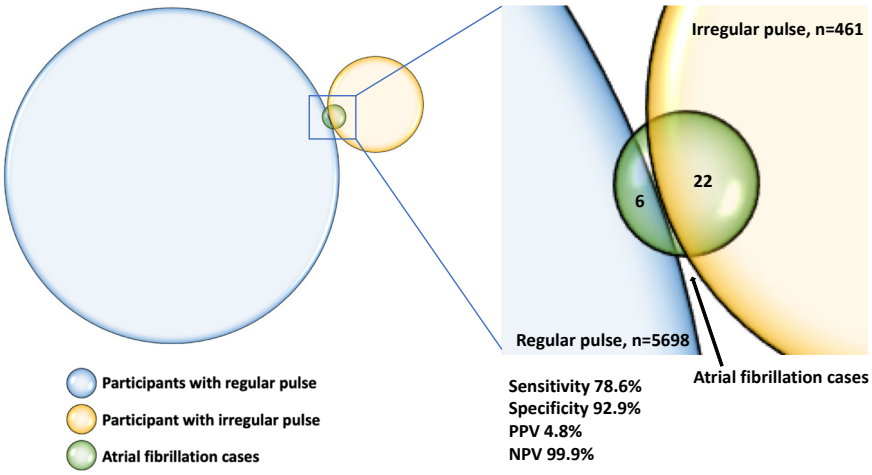

Figure 24. Test performance of pulse palpation.

Sensitivity of pulse palpation was 78.6 %, specificity 92.9 %, positive predictive value 4.8 % and negative predictive value 99.9 %, yielding a total diagnostic accuracy of pulse palpation of 92.8 %, the test performance is shown in Table 9.

Included participants	Participants (n=6159)
Irregular pulse, AF on single-lead ECG (True positives)	22
Regular pulse, no AF on single-lead ECG (True negatives)	5,692
Irregular pulse, no AF on single-lead ECG (False positives)	439
Regular pulse, AF on single-lead ECG (False negatives)	6
Pre-test probability (prevalence)	0.5% (0.3%, 0.7%)
Sensitivity (95% CI)	78.6% (59.0%, 91.7%)
Specificity (95% CI)	92.8% (92.2%, 93.5%)
Positive predictive value (95% CI)	4.8% (3%, 7.1%)
Negative predictive value (95% CI)	99.9% (99.8%, 100%)
Positive likelihood ratio (95% CI)	11.0 (8.7, 13.6)
Negative likelihood ratio (95% CI)	0.23 (0.1, 0.5)
Post-test probability if positive likelihood ratio	5%
Post-test probability if negative likelihood ratio	0%

Table 9. Test performance of pulse palpation compared to single-lead ECG

To diagnose one case of new AF after irregular pulse palpation, 21 ECGs had to be taken. No other significant brady- or tachycardia was identified on the single-lead ECGs.

A sensitivity analysis was done in which 93 of the 137 participants with poor signal quality on the index single-lead ECG but missing a 12-lead ECG were included. Results from the two weeks screening following the screening visit were imputed and in case a new AF had been diagnosed during the two weeks A "worst-case scenario" was defined as if the index-ECG had also shown AF. A "best-case scenario" was defined as if none of the individuals with new AF during two weeks of screening had had AF on the index-ECG. The test performance of pulse palpation for the two different scenarios are shown in Table 10.

	"Worst-case scenario" (n=6252)	"Best-case scenario" (n=6252)
Irregular pulse, AF on single-lead ECG (True positives)	24	22
Regular pulse, no AF on single-lead ECG (True negatives)	5772	5777
Irregular pulse, no AF on single-lead ECG (False positives)	445	447
Regular pulse, AF on single-lead ECG (False negatives)	11	6
Pre-test probability (prevalence)	0.6% (0.4%, 0.8%)	0.4% (0.3%, 0.6%)
Sensitivity (95% CI)	68.6% (50.7%, 83.1%)	78.6% (59%, 91.7%)
Specificity (95% CI)	92.8% (92.2%, 93.5%)	92.8% (92.1%, 93.4%)
Positive predictive value (95% CI)	5.1% (3.3%, 7.5%)	4.7% (3.0%, 7.0%)

Negative predictive value (95% CI)	99.8% (99.7%, 99.9%)	99.9% (99.8%, 100%)
Positive likelihood ratio (95% CI)	9.6 (7.5, 12.2)	10.9 (8.8, 13.5)
Negative likelihood ratio (95% CI)	0.34 (0.2, 0.6)	0.2 (0.1, 0.5)
Post-test probability if positive likelihood ratio	5%	5%
Post-test probability if negative likelihood ratio	0%	0%

Table 10. "Worst case scenario" and "Best case scenario" sensitivity analysis

6.2.2 Symptoms

History of palpitations was found in 1,827/6,159 (29.7%) of the participants. New AF was diagnosed in 11 (0.6%) of the participants with history of palpitations. Most participants reported no history of palpitations, 4,332/6,159 (70.3%) and AF was diagnosed in 14 (0.3%) of them. There was no significant difference in the detection of new AF between symptomatic and asymptomatic participants, see test performance stratified by symptoms in Table 11. In participants diagnosed with new AF, 39% reported having had a history of palpitations.

Included participants	**History of palpitations (n=1827)**	**No history of palpitations (n=4332)**
Irregular pulse, AF on single-lead ECG (True positives)	8	14
Regular pulse, no AF on single-lead ECG (True negatives)	1661	4031
Irregular pulse, no AF on single-lead ECG (False positives)	155	284
Regular pulse, AF on single-lead ECG (False negatives)	3	3
Pre-test probability (prevalence)	0.6% (0.3%, 1.1%)	0.4% (0.2%, 0.6%)
Sensitivity (95% CI)	72.7% (39.0%, 94.0%)	82.4% (56.6%, 96.2%)
Specificity (95% CI)	91.5% (90.1%, 92.7%)	93.4% (92.6%, 94.1%)
Positive predictive value (95% CI)	4.9% (2.1%, 9.4%)	4.7% (2.6%, 7.8%)
Negative predictive value (95% CI)	99.8% (99.5%, 100%)	99.9% (99.8%, 100%)
Positive likelihood ratio (95% CI)	8.5 (5.8, 12.6)	12.5 (9.8, 16)
Negative likelihood ratio (95% CI)	0.3 (0.1, 0.8)	0.2 (0.1, 0.5)
Post-test probability if positive likelihood ratio	5%	5%
Post-test probability if negative likelihood ratio	0%	0%

Table 11. Test performance of pulse palpation stratified by symptoms compared to single-lead ECG

6.3 STUDY III

The overall participation rate in the STROKESTOP II study was 48.6%, a significant increase from the participation in STROKESTOP I in which the uptake was 46.9%in the Stockholm region (p=0.006). Shown in Figure 25 are statistical certainty geomaps of participation in the STROKESTOP I study and the STROKESTOP II study

in Stockholm county displaying, for each of the 99 residential parishes, spatially smoothed participation rates (PRs).

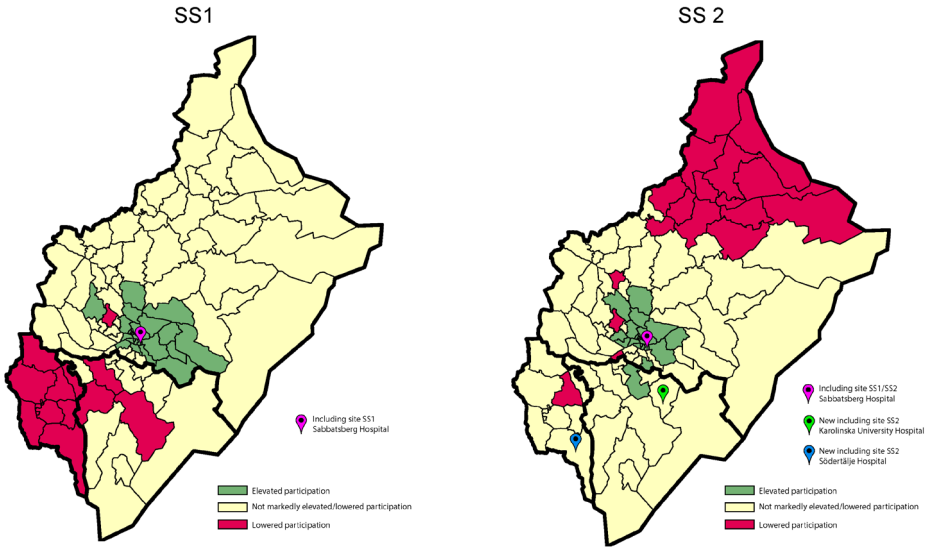

Figure 25. Statistical geo-maps of participation in the STROKESTOP I (SS1) and STROKESTOP II (SS2) studies. 2020 Mar 30;969141320908316. doi: 10.1177/0969141320908316. Online ahead of print. Reprinted by permission of SAGE publications.

The addition of the two new southern Stockholm sites in the STROKESTOP II study increased participation rates in those areas. In comparison the northern region fell out red in the STROKESTOP II study. This was due to increased uptake in the southern part, not because of lower actual uptake rates between the STROKESTOP trials.

When compared to the same catchment areas and corresponding rates from the STROKESTOP I study, the participation rates were significantly higher in the areas where an additional screening site had been added. In the area surrounding the Karolinska University Hospital site the uptake increased from 41% to 47% ($p<0.001$), i.e. a 15% relative increase. In the vicinity of the Södertälje Hospital site, the uptake increased from 28% to 43% ($p<0.001$), i.e. a relative increase of 54%. The uptake was not significantly changed in the catchment area of the Sabbatsberg Hospital site (the one site used in both studies, but with a smaller catchment area in STROKESTOP II), going from 50% in STROKESTOP I to 49% in STROKESTOP II ($p=0.17$). In all three catchment areas, higher participation was observed among women, those with higher education, with higher income, among non-immigrants as well as among married individuals. These results are depicted in Table 12.

	Karolinska University Hospital				Sabbatsberg Hospital				Södertälje Hospital			
	Invited (n)	Partic-ipants (n)	%	p[a]	Invited (n)	Partic-ipants (n)	%	p[a]	Invited (n)	Partic-ipants (n)	%	p[a]
Total												
SS1	1714	705	41		9517	4786	50		618	174	28	
SS2	2086	983	47	<0.001	11240	5544	49	0.17	786	334	43	<0.001
By gender												
Male SS1	802	342	43		4311	2144	50		285	84	29	
Male SS2	976	443	45	0.26	5306	2565	48	0.18	346	145	42	0.002
Female SS1	912	363	40		5260	2642	50		333	90	27	
Female SS2	1110	540	49	<0.001	5934	2979	50	0.99	440	189	43	<0.001
By educational level[b]												
Primary school SS1	585	198	34		2573	1009	39		267	56	21	
Primary school SS2	615	235	38	0.13	2475	912	37	0.09	262	85	32	0.004
Secondary school/higher SS1	1077	497	46		6759	3727	55		303	108	36	
Secondary school/higher SS2	1414	739	52	0.003	8513	4584	54	0.11	470	243	52	<0.001
By disposable income[c]												
Low SS1	964	334	35		4258	1681	39		389	86	22	
Low SS2	854	328	38	0.11	3354	1181	35	<0.001	369	119	32	0.002
Medium SS1	647	315	49		4066	2328	57		189	70	37	
Medium SS2	989	509	51	0.29	5513	2900	53	<0.001	347	176	51	0.003
High SS1	100	54	54		1232	775	63		40	18	45	
High SS2	243	146	60	0.36	2373	1463	62	0.48	70	39	56	0.38
By immigrant background												
Born in Sweden SS1	1199	527	44		7565	4021	53		432	136	31	
Born in Sweden SS2	1551	795	51	<0.001	8952	4690	52	0.34	517	243	47	<0.001
Born outside of Sweden SS1	515	178	35		2006	765	38		186	38	20	
Born outside of Sweden SS2	535	188	35	0.90	2288	854	37	0.61	269	91	34	0.003
By marital status[d]												
Married SS1	948	435	46		5077	2786	55		311	106	34	
Married SS2	1194	617	52	0.009	5981	3209	54	0.21	427	200	47	<0.001
Divorced SS1	354	138	39		2011	906	45		131	32	24	
Divorced SS2	420	175	42	0.49	2626	1172	45	0.80	169	73	43	0.001
Widow/widower SS1	311	107	34		1657	762	46		134	28	21	
Widow/widower SS2	320	132	41	0.09	1499	684	46	0.87	134	46	34	0.02
Unmarried SS1	101	25	25		819	325	40		42	8	19	
Unmarried SS2	152	59	39	0.03	1134	479	42	0.28	56	15	27	0.51

SS2, Strokestop 2 Study; SS1, Strokestop 1 Study
[a] p-value based on the chi-squared test, comparing the participation rates between SS2 and SS1 for a given population group within the specified catchment area.
[b] Data on educational level were missing for 339 invited persons in SS1 and 363 invited persons in SS2.
[c] Data on disposable income were missing for 18 invited persons in SS1.
[d] Data on marital status were missing for 7 invited persons in SS1.

Table 12. Participation rates according to catchment area and socio-demographic characteristics in the STROKESTOP II (SS2) study, compared with corresponding rates in the STROKESTOP I (SS1) study. 2020 Mar 30;969141320908316. doi: 10.1177/0969141320908316. Online ahead of print. Reprinted by permission of SAGE Publications.

The uptake was improved most markedly in the area around the Södertälje Hospital site, where a 1.5-fold increase was observed also in the socioeconomically weaker

population groups (from 21% to 32% participants in the low education group, from 22% to 32% participants in the low-income group and from 31% to 47% participants in the immigrant group).

A univariate logistic regression analysis showed that the odds of participation in the STROKESTOP II study were highest among women, those with higher education, with higher incomes, non-immigrants, married people and those living in the catchment area belonging to the Sabbatsberg Hospital site. The difference in odds ratio in all categories compared to reference was significant. In the multivariable analysis, the odds of attendance were consistent with those in the univariate analysis, except in the catchment area where the difference became insignificant. These results are shown in Table 13.

	Univariate analyses					Multivariable analysis	
Variable	Invited (n)	Participants (n)	%	OR (95% CI)	p[a]	OR (95% CI)	p[a]
Gender					0.02		<0.001
Men	6628	3153	47.6	1.00 (ref)		1.00 (ref))	
Women	7484	3708	49.5	1.08 (1.01, 1.16)		1.43 (1.32, 1.54)	
Educational level					<0.001		<0.001
Primary school	3352	1232	36.8	1.00 (ref)		1.00 (ref)	
Secondary school/higher	10397	5566	53.5	1.98 (1.83, 2.14)		1.65 (1.52, 1.79)	
Unknown	363	63	17.4	0.36 (0.27, 0.48)		0.50 (0.37, 0.66)	
Disposable income					<0.001		<0.001
Low	4577	1628	35.6	1.00 (ref)		1.00 (ref)	
Medium	6849	3585	52.3	1.99 (1.84, 2.15)		1.91 (1.75, 2.07)	
High	2686	1648	61.4	2.88 (2.61, 3.17)		2.58 (2.31, 2.88)	
Immigrant background					<0.001		<0.001
Born outside Sweden	3092	1133	36.6	1.00 (ref)		1.00 (ref)	
Born in Sweden	11020	5728	52.0	1.87 (1.72, 2.03)		1.36 (1.24, 1.48)	
Marital status					<0.001		<0.001
Unmarried	1342	553	41.2	1.00 (ref)		1.00 (ref)	
Widow/widower	1953	862	44.1	1.13 (0.98, 1.30)		0.97 (0.84, 1.13)	
Divorced	3215	1420	44.2	1.13 (0.99, 1.28)		1.06 (0.93, 1.21)	
Married	7602	4026	53.0	1.61 (1.43, 1.81)		1.56 (1.38, 1.76)	
Catchment area					<0.001		0.59
Södertälje Hospital	786	334	42.5	1.00 (ref)		1.00 (ref)	
Karolinska University Hospital	2086	983	47.1	1.21 (1.02, 1.42)		1.07 (0.90, 1.27)	
Sabbatsberg Hospital	11240	5544	49.3	1.32 (1.14, 1.52)		1.02 (0.87, 1.19)	

SS2, Strokestop 2 Study
[a] p-value for variable.

Table 13. Results from logistic regression analysis based on data from the STROKESTOP II study. 2020 Mar 30;969141320908316. doi: 10.1177/0969141320908316. Online ahead of print. Reprinted by permission of SAGE Publications.

6.4 STUDY IV

6.4.1 Non-participants and participants' characteristics

Included in the analysis were 6868 participants and 7086 non-participants. Excluded were individuals who died (n = 340) or emigrated from Sweden (n = 10) prior to having received their last invitation.

Non-participants were more likely to have been hospitalized in the last 5 years, spent more days being hospitalized over the last year prior to index date and were discharged to a retirement home more frequently when compared to participants. The proportion of multimorbid individuals was higher in the non-participants group and they had higher CHA_2DS_2-VASc scores as well as higher Charlson's comorbidity index than the participant group. Non-participants were more likely unmarried, only received primary education, had lower income and were immigrants to a higher degree than the participants.

The prevalence of prior AF in non-participants was significantly higher than in the participants, 17.9% and 8.9% respectively ($p<0.001$). All medical diseases were more prevalent in non-participants than participants.

All types of prescribed medications included in our dataset were more common in non-participants than participants and non-participants had a higher number of unique Anatomical Therapeutic Chemical (ATC)-codes dispensed over the last 3 years than participants. Characteristics of participants vs. non-participants are shown in Table 14.

Characteristics	Non-participants n=7086	Participants n=6868	P-value
General and socioeconomic characteristics			
Female (%)	3703 (52.3)	3710 (54.0)	0,039
Outpatient visits (total over last 5 years) (mean (SD))	16.51 (26.39)	16.15(15.91)	0,330
Hospitalizations (total over last 5 years) (mean (SD))	1.91 (3.44)	1.01 (1.99)	<0.001
Days spent hospitalized last year prior to index (mean (SD))	2.90 (10.48)	0.70 (3.67)	<0.001
Charlson's comorbidity index (weighted) (mean (SD))	1.39 (1.90)	0.95 (1.55)	<0.001
Multimorbidity (%)	1185 (16.7)	943 (13.7)	<0.001
Discharged to retirement home (last 3 years) (%)	181 (2.6)	15 (0.2)	<0.001
Marital status: Married (%)	3454 (48.7)	3977 (57.9)	<0.001
Marital status: Unmarried (%)	759 (10.7)	552 (8.0)	<0.001

Marital status: Divorced (%)	1737 (24.5)	1416 (20.6)	<0.001
Marital status: Widowed (%)	1136 (16.0)	923 (13.4)	<0.001
Educational attainment: Tertiary (%)	1902 (26.8)	2799 (40.8)	<0.001
Educational attainment: Secondary (%)	2809 (39.6)	2774 (40.4)	0,376
Educational attainment: Primary (%)	2079 (29.3)	1232 (17.9)	<0.001
Educational attainment: Missing (%)	296 (4.2)	63 (0.9)	<0.001
Disposable income: Low (%)	2681 (37.8)	1519 (22.1)	<0.001
Disposable income: Medium (%)	3413 (48.2)	3823 (55.7)	<0.001
Disposable income: High (%)	992 (14.0)	1526 (22.2)	<0.001
Born in Sweden (%)	5162 (72.8)	5734 (83.5)	<0.001
Medical history			
Ischemic stroke (%)	547 (7.7)	242 (3.5)	<0.001
Total atrial fibrillation prevalence (%)	1267 (17.9)	610 (8.9)	<0.001
Medicated atrial fibrillation (on OAC treatment) (%)	1178 (16.6)	551 (8.0)	<0.001
CHA_2DS_2-VASc score (mean (SD))	3.68 (1.33)	3.27 (1.07)	<0.001
Pulmonary embolism (%)	162 (2.3)	109 (1.6)	0,003
Thromboembolism (%)	955 (13.5)	553 (8.1)	<0.001
Intracerebral bleeding (%)	97 (1.4)	32 (0.5)	<0.001
Other intracranial bleeding (%)	146 (2.1)	79 (1.2)	<0.001
Hospitalization due to bleeding (%)	833 (11.8)	479 (7.0)	<0.001
Anaemia (%)	738 (10.4)	365 (5.3)	<0.001
Myocardial infarction (%)	743 (10.5)	376 (5.5)	<0.001
Vascular disease (%)	743 (10.5)	376 (5.5)	<0.001
Peripheral artery disease (%)	465 (6.6)	228 (3.3)	<0.001
Heart failure (%)	771 (10.9)	269 (3.9)	<0.001
Mitral stenosis (%)	14 (0.2)	8 (0.1)	0,32
Mechanical prosthetic valve (%)	50 (0.7)	23 (0.3)	0,004
Pacemaker (%)	288 (4.1)	133 (1.9)	<0.001
Hypertension (%)	3373 (47.6)	2387 (34.8)	<0.001
Hyperlipidemia (%)	1199 (16.9)	915 (13.3)	<0.001
Diabetes (%)	1408 (19.9)	845 (12.3)	<0.001
Liver disease (%)	156 (2.2)	90 (1.3)	<0.001
Chronic kidney disease (%)	331 (4.7)	129 (1.9)	<0.001
Hypothyroidism (%)	397 (5.6)	351 (5.1)	0,21
Thyrotoxicosis (%)	12 (0.2)	13 (0.2)	0,938
Chronic obstructive pulmonary disease (%)	641 (9.0)	278 (4.0)	<0.001
Rheumatoid arthritis (%)	157 (2.2)	146 (2.1)	0,76
Osteoarthritis (%)	1602 (22.6)	1826 (26.6)	<0.001
Alcohol index (%)	414 (5.8)	141 (2.1)	<0.001

Dementia (%)	461 (6.5)	70 (1.0)	<0.001
Cancer (last 3 years) (%)	819 (11.6)	637 (9.3)	<0.001
Parkinson's disease (%)	257 (3.6)	156 (2.3)	<0.001
Psychiatric diseases (%)	531 (7.5)	254 (3.7)	<0.001
Medicine dispensations			
Anticoagulants (%)	3251 (45.9)	2162 (31.5)	<0.001
Psychiatric medications (%)	1366 (19.3)	736 (10.7)	<0.001
Neuroleptics (%)	279 (3.9)	54 (0.8)	<0.001
Parkinson's disease medications (%)	227 (3.2)	118 (1.7)	<0.001
COPD medication (%)	1186 (16.7)	943 (13.7)	<0.001
Diabetes medications and insulin (%)	1164 (16.4)	672 (9.8)	<0.001
Antihypertensives (%)	92 (1.3)	70 (1.0)	0,144
Diuretics (%)	1637 (23.1)	1058 (15.4)	<0.001
Beta blockers (%)	2927 (41.3)	1934 (28.2)	<0.001
Calcium antagonists (%)	2130 (30.1)	1582 (23.0)	<0.001
RAAS inhibitors (%)	3597 (50.8)	3017 (43.9)	<0.001
Lipid lowering agents (%)	2794 (39.4)	2296 (33.4)	<0.001
Unique ATC-codes with repeated consumption (last 3 years) (mean (SD))	8.92 (6.97)	7.23 (5.69)	<0.001

Table 14. Characteristics of non-participants versus participants.

6.4.2 Factors predicting participation

The twenty-five most important variables predicting participation are shown in Figure 26. Low disposable income was the variable with the strongest influence on participation. It had a very negative influence on participation. The frequency of hospitalisations had a negative proportional influence on participation - the more hospitalisations, the lower the participation rate. Similarly, the higher the CHA_2DS_2-VASc score was the more negative influence it had on participation. Tertiary education was the fifth most important variable, but it was the first one with a positive influence on participation. Dementia was the disease with the strongest negative influence on the participation and the seventh most important variable.

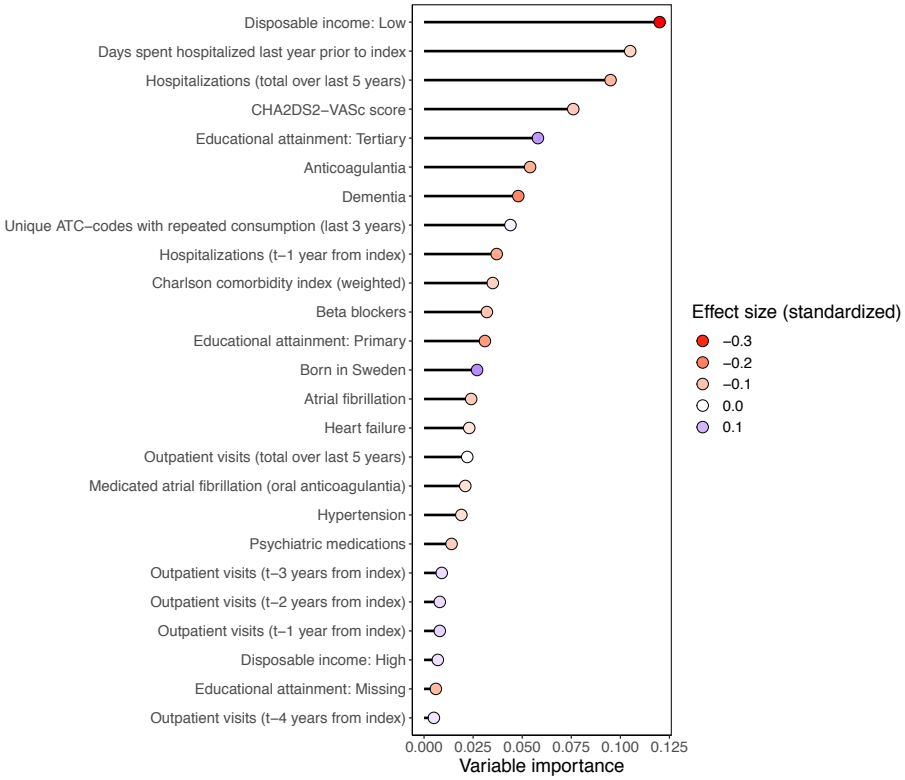

Figure 26. Variable importance for predicted participation

When all individuals in the intention-to-screen group were divided into quartiles according to the propensity score for participation, individuals in the quartile 1 (Q1) had the lowest propensity score for participation and individuals in quartile 4 (Q4) had the highest propensity score for participation. Individuals in Q1 had the lowest socioeconomic status, more medical conditions and had the highest amount of prescription medicine dispensing whereas the opposite applied to the individuals in Q4. This is shown in Table 15.

Propensity score quartiles:	Q1 (0.128, 0.379) n=3489	Q2 (0.379, 0.496) n=3488	Q3 (0.496, 0.607) n=3488	Q4 (0.607, 0.796) n=3489	**P-value**
General characteristics					
Female (%)	1860 (53.3)	1758 (50.4)	1891 (54.2)	1904 (54.6)	0,002
Outpatient visits (total over last 5 years) (mean (SD))	18.05 (33.22)	16.62 (20.48)	15.85 (15.53)	14.79 (11.98)	<0.001
Hospitalizations (total over last 5 years) (mean (SD))	3.23 (4.63)	1.42 (2.03)	0.83 (1.36)	0.40 (0.72)	<0.001

Days spent hospitalized last year prior to index (mean (SD))	6.20 (14.85)	0.70 (2.60)	0.26 (1.08)	0.10 (0.51)	<0.001
Charlson's comorbidity index (weighted) (mean (SD))	1.84 (2.07)	1.32 (1.74)	1.01 (1.64)	0.53 (1.16)	<0.001
Multimorbidity (%)	843 (24.2)	505 (14.5)	401 (11.5)	379 (10.9)	<0.001
Discharged to retirement home (last 3 years) (%)	173 (5.0)	21 (0.6)	1 (0.0)	1 (0.0)	<0.001
Marital status: Married (%)	1518 (43.5)	1832 (52.5)	1945 (55.8)	2136 (61.2)	<0.001
Marital status: Unmarried (%)	399 (11.4)	360 (10.3)	316 (9.1)	236 (6.8)	<0.001
Marital status: Divorced (%)	952 (27.3)	821 (23.5)	713 (20.4)	667 (19.1)	<0.001
Marital status: Widowed (%)	620 (17.8)	475 (13.6)	514 (14.7)	450 (12.9)	<0.001
Educational attainment: Tertiary (%)	462 (13.2)	922 (26.4)	1310 (37.6)	2007 (57.5)	<0.001
Educational attainment: Secondary (%)	1341 (38.4)	1518 (43.5)	1420 (40.7)	1304 (37.4)	<0.001
Educational attainment: Primary (%)	1392 (39.9)	1014 (29.1)	736 (21.1)	169 (4.8)	<0.001
Educational attainment: Missing (%)	294 (8.4)	34 (1.0)	22 (0.6)	9 (0.3)	<0.001
Disposable income: Low (%)	2048 (58.7)	1341 (38.4)	708 (20.3)	103 (3.0)	<0.001
Disposable income: Medium (%)	1249 (35.8)	1699 (48.7)	2018 (57.9)	2270 (65.1)	<0.001
Disposable income: High (%)	192 (5.5)	448 (12.8)	762 (21.8)	1116 (32.0)	<0.001
Born in Sweden (%)	2135 (61.2)	2593 (74.3)	2977 (85.3)	3191 (91.5)	<0.001
Medical history					
Ischemic stroke (%)	434 (12.4)	250 (7.2)	92 (2.6)	13 (0.4)	<0.001
Atrial fibrillation (%)	960 (27.5)	742 (21.3)	163 (4.7)	12 (0.3)	<0.001
Medicated atrial fibrillation (on OAC) (%)	917 (26.3)	697 (20.0)	115 (3.3)	0 (0.0)	<0.001
CHA_2DS_2-VASc score (mean (SD))	4.19 (1.50)	3.72 (1.17)	3.24 (0.91)	2.75 (0.65)	<0.001
Pulmonary embolism (%)	112 (3.2)	68 (1.9)	60 (1.7)	31 (0.9)	<0.001
Thromboembolism (%)	709 (20.3)	490 (14.0)	255 (7.3)	54 (1.5)	<0.001
Intracerebral bleeding (%)	68 (1.9)	41 (1.2)	14 (0.4)	6 (0.2)	<0.001
Other intracranial bleeding (%)	113 (3.2)	64 (1.8)	34 (1.0)	14 (0.4)	<0.001
Hospitalisation due to bleeding (%)	613 (17.6)	346 (9.9)	241 (6.9)	112 (3.2)	<0.001
Anaemia (%)	584 (16.7)	266 (7.6)	164 (4.7)	89 (2.6)	<0.001
Myocardial infarction (%)	609 (17.5)	372 (10.7)	123 (3.5)	15 (0.4)	<0.001
Vascular disease (%)	609 (17.5)	372 (10.7)	123 (3.5)	15 (0.4)	<0.001
Peripheral artery disease (%)	315 (9.0)	226 (6.5)	115 (3.3)	37 (1.1)	<0.001
Heart failure (%)	739 (21.2)	261 (7.5)	37 (1.1)	3 (0.1)	<0.001

Mitral stenosis (%)	18 (0.5)	4 (0.1)	0 (0.0)	0 (0.0)	<0.001
Mechanical prosthetic valve (%)	44 (1.3)	20 (0.6)	8 (0.2)	1 (0.0)	<0.001
Pacemaker (%)	236 (6.8)	123 (3.5)	45 (1.3)	17 (0.5)	<0.001
Hypertension (%)	2054 (58.9)	1911 (54.8)	1306 (37.4)	489 (14.0)	<0.001
Hyperlipidemia (%)	787 (22.6)	702 (20.1)	461 (13.2)	164 (4.7)	<0.001
Diabetes (%)	973 (27.9)	702 (20.1)	467 (13.4)	111 (3.2)	<0.001
Liver disease (%)	92 (2.6)	78 (2.2)	50 (1.4)	26 (0.7)	<0.001
Chronic kidney disease (%)	267 (7.7)	116 (3.3)	57 (1.6)	20 (0.6)	<0.001
Hypothyroidism (%)	259 (7.4)	213 (6.1)	178 (5.1)	98 (2.8)	<0.001
Thyrotoxicosis (%)	8 (0.2)	5 (0.1)	8 (0.2)	4 (0.1)	0,563
Chronic obstructive pulmonary disease (%)	471 (13.5)	253 (7.3)	132 (3.8)	63 (1.8)	<0.001
Rheumatoid arthritis (%)	80 (2.3)	90 (2.6)	76 (2.2)	57 (1.6)	0,052
Osteoarthritis (%)	803 (23.0)	877 (25.1)	865 (24.8)	883 (25.3)	0,098
Alcohol index (%)	257 (7.4)	155 (4.4)	122 (3.5)	21 (0.6)	<0.001
Dementia (%)	501 (14.4)	30 (0.9)	0 (0.0)	0 (0.0)	<0.001
Cancer (last 3 years) (%)	408 (11.7)	406 (11.6)	372 (10.7)	270 (7.7)	<0.001
Parkinson's disease (%)	129 (3.7)	105 (3.0)	115 (3.3)	64 (1.8)	<0.001
Psychiatric diseases (%)	359 (10.3)	204 (5.8)	152 (4.4)	70 (2.0)	<0.001
Medicine dispensations					
Anticoagulants (%)	2054 (58.9)	1907 (54.7)	1134 (32.5)	318 (9.1)	<0.001
Psychiatric medications (%)	945 (27.1)	506 (14.5)	450 (12.9)	201 (5.8)	<0.001
Neuroleptics (ATC: N05A) (%)	224 (6.4)	70 (2.0)	35 (1.0)	4 (0.1)	<0.001
Parkinson's disease medications (%)	117 (3.4)	88 (2.5)	88 (2.5)	52 (1.5)	<0.001
COPD medication (%)	718 (20.6)	549 (15.7)	486 (13.9)	376 (10.8)	<0.001
Diabetes medications and insulin (%)	795 (22.8)	571 (16.4)	383 (11.0)	87 (2.5)	<0.001
Antihypertensives (%)	58 (1.7)	54 (1.5)	29 (0.8)	21 (0.6)	<0.001
Diuretics (%)	1144 (32.8)	769 (22.0)	522 (15.0)	260 (7.5)	<0.001
Beta blockers (%)	1786 (51.2)	1771 (50.8)	1000 (28.7)	304 (8.7)	<0.001
Calcium antagonists (%)	1127 (32.3)	1160 (33.3)	969 (27.8)	456 (13.1)	<0.001
RAAS inhibitors (%)	1920 (55.0)	1962 (56.2)	1672 (47.9)	1060 (30.4)	<0.001
Lipid lowering agents (%)	1660 (47.6)	1547 (44.4)	1211 (34.7)	672 (19.3)	<0.001
Unique ATC-codes with repeated consumption (last 3 years) (mean (SD))	10.97 (8.21)	8.90 (6.07)	7.38 (5.29)	5.10 (3.83)	<0.001
Unique ATC-codes with repeated consumption (last 3 years) (mean (SD))	10.97 (8.21)	8.90 (6.07)	7.38 (5.29)	5.10 (3.83)	<0.001

Table 15. Characteristics of the intention-to-treat group stratified into quartiles by propensity score for participation

When comparing inpatient and outpatient visits between the non-participants and participants over the last five year prior to index date, the non-participants had an increasing amount of hospitalizations over the years whereas the participants seemed to be on a plateau level. There was, however, no difference in outpatient visits between the groups, see Figure 27.

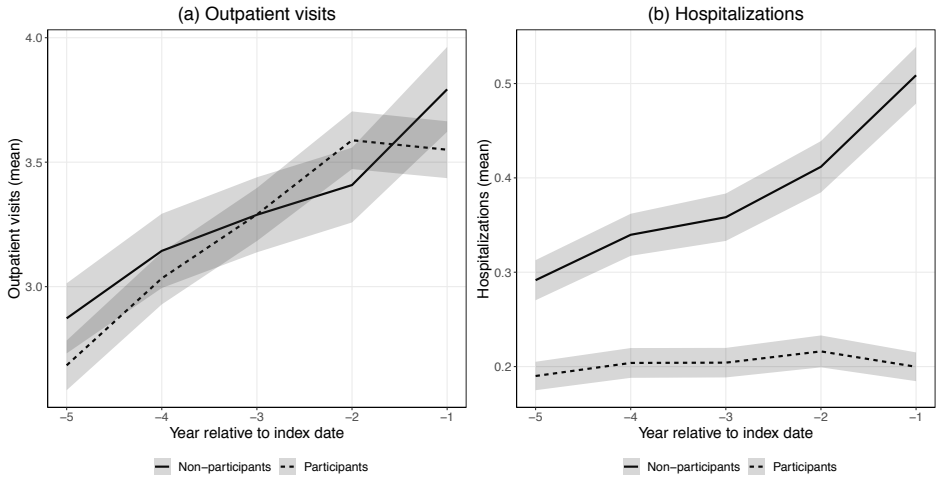

Figure 27. Outpatient visits and hospitalizations in participants and non-participants over the last five years prior to index date

6.4.3 Potential yield of detection: Total AF prevalence and untreated AF prevalence

Observed prevalence of prior AF, unmedicated, new AF and untreated AF for participants, and estimated prevalence among non-participants and in the entire population are shown in Table 16.

All participants	Invited population (est via ATE weights	Non-participants (est via ATU weights)	Participants	Difference (Participants - non-participants)	**Ratio (Participants / non-non-participants)**
Prior AF	12.41 (11.53, 13.34)	15.47 (14.36, 16.65)	9,54	-5,93	0,62
Unmedicated prior AF	1.06 (0.83, 1.35)	1.14 (0.88, 1.49)	0,98	-0,17	0,85
New AF	2.34 (1.98, 2.77)	2.41 (1.97, 2.95)	2,27	-0,14	0,94
Untreated AF	3.4 (2.96, 3.9)	3.56 (3.03, 4.17)	3,25	-0,31	0,91

CHA_2DS_2-VASc = 2 (Women - 1) n = 3864	**Invited population (est via ATE weights)**	**Non-participants (est via ATU weights)**	**Par-tici-pants**	**Difference (Participants – non-par-ticipants)**	**Ratio (Partic-ipants / non-par-ticipants)**
Prior AF	4.76 (4.07, 5.56)	5.73 (4.87, 6.74)	4,01	-1,72	0,7
Unmedicated AF	1.01 (0.72, 1.42)	1.15 (0.81, 1.65)	0,91	-0,25	0,78
New AF	2.56 (2.04, 3.19)	2.79 (2.09, 3.7)	2,38	-0,4	0,85
Untreated AF	3.57 (2.97, 4.29)	3.94 (3.14, 4.93)	3,29	-0,65	0,83
CHA_2DS_2-VASc = 3 (Women - 1) n = 1735	**Invited population (est via ATE weights)**	**Non-participants (est via ATU weights)**	**Par-tici-pants**	**Difference (Participants - non-partic-ipants)**	**Ratio (Partic-ipants / non-par-ticipants)**
Prior AF	14.75 (13.01, 16.67)	17.16 (15.12, 19.41)	12,39	-4,77	0,72
Unmedicated AF	1.33 (0.87, 2.02)	1.39 (0.89, 2.16)	1,27	-0,12	0,91
New AF	2.42 (1.8, 3.25)	2.31 (1.69, 3.15)	2,54	0,23	1,1
Untreated AF	3.75 (2.94, 4.76)	3.69 (2.86, 4.75)	3,8	0,11	1,03
CHA_2DS_2-VASc = 4 (Women - 1) n = 747	**Invited population (est via ATE weights)**	**Non-participants (est via ATU weights)**	**Par-tici-pants**	**Difference (Participants - non-partic-ipants)**	**Ratio (Partic-ipants / non-par-ticipants)**
Prior AF	22.94 (19.83, 26.38)	25.66 (22.18, 29.48)	19,41	-6,25	0,76
Unmedicated AF	1.1 (0.51, 2.32)	1.22 (0.56, 2.65)	0,94	-0,28	0,77
New AF	2 (1.17, 3.42)	2.1 (1.18, 3.72)	1,87	-0,23	0,89
Untreated AF	3.1 (2, 4.77)	3.32 (2.09, 5.23)	2,81	-0,51	0,85
CHA_2DS_2-VASc >= 5 (Women - 1) n = 522	**Invited population (est via ATE weights)**	**Non-participants (est via ATU weights)**	**Par-tici-pants**	**Difference (Participants - non-partic-ipants)**	**Ratio (Partic-ipants / non-par-ticipants)**
Prior AF	31.64 (27.5, 36.09)	34.66 (30.16, 39.47)	26,82	-7,84	0,77
Unmedicated AF	0.54 (0.17, 1.73)	0.53 (0.15, 1.77)	0,57	0,05	1,09
New AF	1.47 (0.63, 3.37)	1.67 (0.69, 3.99)	1,15	-0,52	0,69
Untreated AF	2.01 (1.01, 3.97)	2.19 (1.05, 4.51)	1,72	-0,47	0,79
(est via ATU weights)	Participants	Difference			
(Participants - non-par-ticipants)	Ratio (Participants / non-participants)				

Table 16. Observed prevalence of prior AF, unmedicated prior AF, new AF and untreated AF sorted by CHA_2DS_2-VASc score for participants, and estimated prevalence among non-participants and in the entire intention-to-screen population

The weighted estimates imply that the non-participants had 38% higher prevalence of known AF. The weighted estimates also imply that if the non-participants had participated the proportion of new AF would have been 2.4% in this group compared to 2.3% in the participants. The proportion of untreated AF among non-participants was estimated to 3.6% compared to 3.3% in the participants.

When stratifying the intention-to-screen group into CHA_2DS_2-VASc scores 2, 3, 4, and >5 (- 1 point for females) the proportion of non-participants with prior AF grew with rising CHA_2DS_2-VASc score from 5.7% in the group with CHA_2DS_2-VASc score 2 to 34.7% in the group with CHA_2DS_2-VASc scores >5. The same applied to the participants, although the proportions were lower. The largest difference in untreated AF between participants and non-participants was found in the group with CHA_2DS_2-VASc score 2.

The outcome of untreated AF versus the propensity score of participation is shown in Figure 28. There was a trend towards a higher proportion of untreated AF in the lower propensity score levels for participation, but large confidence intervals make it difficult to make any inference on the relationship.

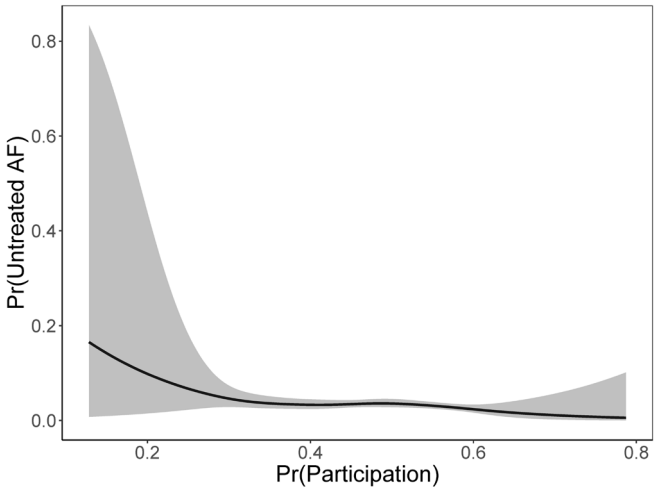

Figure 28. Outcome of untreated AF vs. the propensity score of participation

7 DISCUSSION

7.1 MAJOR FINDINGS

In the first study, we found new AF in 4.4% of the participants in the high-risk group (NT-proBNP ≥125 ng/L), increasing the total prevalence of AF in all participants from 8.1% to 10.5%. Furthermore, 41% of the participants had low NT-proBNP levels (<125ng/L) and were only screened with one index single-lead ECG at the visit. In multivariable analysis of the high-risk group, NT-proBNP was the strongest predictor for new AF.

In the second study, we found that pulse palpation had a low positive predictive value. For every irregular pulse palpated, 20 ECGs had to be taken to confirm one case of AF. The sensitivity of pulse palpation was modest. Almost one-third of the participants reported having a history of palpitations, but this did not predict new AF detection.

In the third study, we found that geographic distance to screening sites is of importance and by increasing the number of screening sites, screening participation can be significantly increased, even in groups of lower socioeconomic status. Socio-demographic factors have a significant impact on the screening participation.

In the fourth study, we found the hypothetical yield of new AF and untreated AF if the non-participants had attended screening was higher compared to the participants group. More individuals with high CHA_2DS_2-VASc scores were estimated to be in the non-participant group, underlining the fact that the non-participants would probably benefit from screening in case of new AF diagnosis, as they would be candidates for OAC treatment. We found that the non-participants could generally be considered poorer in health, of lower socioeconomic status and less mobile than the participants.

7.2 SCREENING FOR ATRIAL FIBRILLATION

Screening for AF seems to fit most of Wilson and Junger's criteria for screening which are still considered the "gold standard" when considering screening for a particular disease. No less important is the statement, *"The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement (on the one hand, bringing to treatment those with previously undetected disease and, on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes it may appear deceptively easy." (Principles and practice of screening for disease, 1968) (15)*

A great deal of research is needed to determine which criteria should be used and

what processes are required to ensure that new screening programmes best serve the public interest. There is a growing amount of interest in screening for AF as it seems to check the right boxes for screening criteria, but there are knowledge gaps that have to be filled before taking action against this growing global epidemic. The most important gap to be filled is the lack of evidence that screening-detected AF and initiation of OAC treatment when indicated, reduces incidence or severity of stroke.

In recent years many studies have been published on the topic of AF screening: the differences and advantages of opportunistic vs. systematic screening, different AF detection modalities and AF detection in different population groups, to name a few. In 2017 a white paper from the AF SCREEN international collaboration made a case for AF screening while recognising that randomised controlled trials with hard endpoints are still awaited (123).

7.2.1 Systematic vs. opportunistic screening

Opportunistic screening is recommended (class I level B recommendation) in international guidelines and can be undertaken at relatively low cost by pulse taking, 12-lead ECG or ECG rhythm strips for 30 seconds (8). Opportunistic screening has been considered to carry lower cost than systematic screening (21). The AF yield of single-time-point screening in >65-year-olds was 1,4% in a systematic review (124). Regardless of screening setting and considering that the majority of those identified had sufficiently high stroke risk to benefit from thromboprophylaxis, that has the potential to reduce stroke burden in societies. Both opportunistic and systematic screening were more cost-effective than routine practice in >65-year-olds (125).

Systematic screening should be considered (class II level A recommendation) in individuals >75-years of age or in those at high risk of stroke according to the 2020 ESC AF Guidelines (8). Whether systematic screening is superior to opportunistic screening is an unanswered question, but randomised clinical trials are underway such as the STROKESTOP trials amongst others (10, 126). Because AF prevalence is on the rise and AF complications are predicted to increase over the next decades, such studies are important. While stroke is usually the primary end point being studied, an effect on all-cause mortality could be expected and also potentially on heart failure, myocardial infarction, and dementia could be expected. Hopefully, the ongoing and planned studies will provide these answers.

A meta-analysis by Petryszyn et al. assessed the effectiveness of AF screening and its determinants and found that active screening for AF, whether it be systematic or opportunistic, was effective from 40 years of age. The organisation of the screening process seemed to be more important than the screening modalities. In a subgroup

analysis systematic screening was superior to opportunistic screening in identifying previously unknown AF (78).

7.2.2 Whom to screen

The prevalence of AF increases with age (25). That fact makes screening for AF less cost-efficient in a population where the prevalence is too low. Also, the treatment of the disease-in this case OAC treatment for stroke prevention-should be an option for those with newly discovered AF, and this is not always the case in younger individuals. In the Apple Heart Study 0,52% of the participants had irregular pulse and were offered to wear an ECG patch, of which 21% consented to. The AF yield in the age group >65 years was 35%, whereas in the age group <40 years it was 18%. In total 0.04% were found to have AF of all participants (127). In study IV we found that the non-participants were not as mobile or as healthy as the participants in the STROKESTOP II study and untreated AF was higher in that group, underlining that this would be a group that would probably benefit from AF screening. For policy makers it is important that a screening program has clear health benefits and is cost-effective. A simulation model designed to find the optimal screening program in Swedish settings found that the most optimal program for AF screening, when all the possible designs of screening programs were considered, was screening at the age of 75 years with the lowest cost per gained QALY (71). In both of the STROEKSTOP studies, 75/76-year-olds are invited for screening due to the fact that they are candidates for OAC treatment by age alone (10, 126). Screening at the high age of 75 can offer specific logistic problems since some individuals are bound to be frail or multimorbid. There are few systematic screening programs conducted in this specific age group, although the Danish LOOP study included individuals >70 years of age with one or more risk factor for stroke (73) and the SAFER trial invited individuals >70 years of age to participate (74). A Norwegian AF screening and prevalence study achieved a very high uptake in a 75-year old population using home visits, resulting in a higher uptake (82%) in this age-group (105). Current medical screening programs in Sweden are targeting lower age groups and these programs are reporting considerable higher uptake than the one reported from the STROKESTOP trials, implying that age and frailty are factors contributing to participation (128).

7.2.3 Benefits and harms of screening

Screenings amongst the elderly is a way of searching within a population that has a higher prevalence of AF and more often these individuals have a higher CHA_2DS_2-VASc score, implicating they would probably benefit from OAC treatment. Inci-

dentally found AF also seems to respond in the same way as clinically detected, so it seems logical that screening-detected AF would behave much the same (11). The most obvious benefit of screening to find AF in high-risk individuals would be the possible prevention of stroke. Other factors that could come from detecting AF through screening could be the possibility of preventing or early reversal of atrial remodelling, tachycardia induced cardiomyopathy, other AF related morbidity such as dementia, hospitalisations and mortality.

There are several potential harms that could come from AF screening. No screening tests report 100% sensitivity and specificity so there is always risk for false positives and false negatives. False positive tests could possibly cause overdiagnosis and overtreatment. A false negative test, on the other hand, could give false security as well as an untreated disease. There might be negative consequences and anxiety caused by being diagnosed with a disease; although, appropriate patient information and screening program organisation may reduce that anxiety. The UK SAFE study found higher levels of anxiety among participants that were diagnosed with AF, although the screening was tolerated by most (67). The risk of bleeding from OAC treatment is an important harm, a potentially life threatening one and that should be considered before initiating OAC treatment in any circumstances. The cost for the healthcare system by choosing to allocate resources to implement this intervention could be greater than the cost gained. These are all important points to consider either before or when screening may become a planned program. The United States Preventive Service Task Force (USPSTF) recommended against screening for AF and mainly based on lack of randomised controlled trials on stroke reduction as well as the concern that downstream treatment as a consequence of the screening could lead to complications otherwise not encountered (76). The Swedish authorities have also recommended against screening for AF using similar reasoning (129).

7.3 OAC INITIATION AND ADHERENCE

Almost 95% of the participants in Study I accepted initiation of OAC, and of those 96% were still adherent to the treatment at one-year follow-up. This is in accordance with our previous results from AF screening trials (10). The high acceptance is likely at least partly be due to a predefined care pathway within the trial, which is something the 2020 ESC AF guidelines recommend (8). A dedicated research team taking responsibility for the entire screening process could, of course, affect the participants' willingness to accept OAC therapy. Referring the patient outside the screening context, however, has been associated with lower OAC initiation rates (130). Participants with previously known AF had OAC treatment to a higher extent

in Study I than in STROKESTOP I (10). In study I the patients with new AF who were initiated on OAC treatment were to a very large extent (96%) adherent to the treatment after one year. These number are somewhat higher than those from another study from Stockholm, in which analysis of OAC treatment in AF patients between 2011 and 2014 found 88.2% of AF patients adherent to OAC treatment after one year (131). Both the OAC acceptance and adherence in our studies is in line with considerable increase in OAC use in Sweden during the last five years (132).

7.4 NT-PROBNP IN ATRIAL FIBRILLATION SCREENING

Several previous studies have shown NT-proBNP to be a powerful predictor of incident AF as well as being a predictor for increased risk of stroke and death (133-136). This combination makes it a candidate for a biomarker to aid the decision on how to find those individuals at the highest risk and whom to screen for AF. Data from 58,173 individuals in Europe with almost eight years median follow-up time found that patients with NT-proBNP over 82.2ng/L had twice the risk of both ischaemic and haemorrhagic stroke compared to those with NT-proBNP <20.4ng/L, confirming that NT-proBNP can be valuable in identifying those at higher risk for stroke (137).

The cut-off of 125ng/L used in the STROKESTOP II study was derived from a sub-study to the STROKESTOP I study. After analysing NT-proBNP levels in about 900 participants, it was found that using NT-proBNP of 125ng/L as cut-off would mean that 35% fewer participants would have had to undergo prolonged screening. This would reduce the cost of ECG equipment and interpretation as a result and miss at most a quarter of new AF cases (108). Based on these results, the hypothesis for the STROKESTOP II study was that stepwise screening with NT-proBNP would identify high-risk individuals for both AF, stroke and death.

Although the low-risk group in study I was not investigated with repeated ECG recordings and some new AF cases probably went undetected in that group, the proportion of participants diagnosed with AF on index ECG was markedly higher in the high-risk group, possibly confirming the discriminative performance of NT-proBNP.

NT-proBNP has repeatedly been shown to be one of the strongest predictors for AF development (100). When adding NT-proBNP to the multivariable analyses, heart failure became an insignificant factor for AF prediction in study I. This finding is similar to the findings of Hijazi et al. that clinical factors such as heart failure, diabetes, hypertension, other cardiovascular diseases and gender no longer added prognostic value after adding biomarkers to the ABC-stroke risk score (46). Our results confirm those findings and call attention to the important addition of biomarkers such as NT-proBNP for improved AF screening.

In a sub-study to the STROKESTOP II study, characteristics of participants with high NT-proBNP (>900ng/L) but no prior heart failure were described (138). Of 93 participants, 30% had new AF and an additional 14% were found to have other clinically relevant cardiovascular comorbidities, indicating that higher levels of NT-proBNP justify further clinical investigation.

7.5 DIAGNOSTIC PERFORMANCE OF SCREENING MODALITIES

The ESC AF Guidelines have since 2012 recommend pulse palpation or a rhythm strip in opportunistic screening for AF (8). Pulse palpation is a readily available, low-cost triage test that needs verification with ECG in case of irregular pulse. In Study II, we found a lower sensitivity (78.6%) than Hobbs et al. found in the SAFE study (87.2%) (67). Lower sensitivity means a higher false negative rate, which is regarded as an undesirable effect in a triage test because it means we would miss out on a disease that is present. The negative effects of failure to recognise AF, and thereby increasing the patient's risk for stroke cannot be stressed enough. A study performed in a real-life setting in general practice in Denmark where a 12-lead ECG was performed in case of irregular pulse showed a similarly low positive predictive value for the pulse palpation test (5.1 %) in the age group 75-84 years (139). When asking patients to palpate their own pulse and register as regular or irregular before recording a single-lead ECG in a multicentre primary care study in Sweden, sensitivity was only 25 % per measurement occasion (20). Tests of irregular pulse are triage tests, whereas single-lead ECG devices have shown good diagnostic accuracy (10, 140). Recording a single-lead ECG takes about the same amount of time to perform as pulse palpation, but the diagnosis can be confirmed instantly in most cases.

Improved AF detection in high-risk individuals has the potential of reducing AF-related stroke and in recent years new rhythm-monitoring technologies have been evolving quickly. A review from 2018 examined the evidence supporting the use of some of the newer technologies (79) and in an era of rapid technological advances and the many emerging new instruments for detecting irregular pulse as well as easy to use single-lead ECG recordings, there might be room for more precise methods than pulse palpation. The medical society and research cannot always keep up with new technology; nonetheless, focus needs to be on evidence-based medicine, and accuracy studies are important. It is up to the medical community to sort out the different options and make educated recommendations to patients and health care systems. In the recent 2020 ESC AF Guidelines patient participation and patient-centered health care is stressed. Additionally, mobile technology with the

possibility of providing practices with easy-to-use rhythm devices and the public with self-screening devices is most likely going to be a part of that goal (8).

7.6 SYMPTOMS OF PALPITATIONS IN ATRIAL FIBRILLATION SCREENING

Palpitations are the most common symptom in AF patients (64, 141). The proportion of individuals in Study II that had new AF and reported history of palpitations was 39 %, similar to what Siontis et al. found (40%) in their study on patients with previously known AF (64). Asymptomatic AF patients appear to have a higher risk of stroke and one-year mortality than symptomatic patients (142). Asymptomatic patients should be treated based on the same principles as symptomatic patients, and efforts should be put into treating concomitant conditions. OAC treatment should also be initiated if indicated (143).

In clinical practice, patients reporting symptoms of palpitations could be assessed by pulse palpation as a triage test, but our results from Study II show that the post-test probabilities of pulse palpation do not change with symptoms. Hence, history of palpitations did not predict new AF detection.

7.7 SCREENING PARTICIPATION AND SCREENING PARTICIPANTS

For any screening to be successful, individuals have to participate, regardless of their socioeconomic status, health status or other specific characteristics. Studies III and IV focus on both socioeconomic and medical characteristics of the participants compared to non-participants in the STROKESTOP II study.

In Study III we illustrated that geographic distance to the screening site was of high importance and that increasing the number of sites has the potential to significantly increase uptake in screening studies. In the Danish VIVA study, a population study on screening for vascular disease, specially trained nurses operated mobile clinics in hospitals, general practitioners' offices or even in a town hall, resulting in an uptake of 74.7% among men aged 65-74 years (104). We also found that sociodemographic factors had a significant impact on AF-screening-program participation. As in the STROKESTOP I study, the individuals with the highest odds of attending were those with higher education, high income, those who were married and non-immigrants (103). In Study IV we found that the factor with the strongest negative influence on participation was low income. This confirms results from a previous study by Zarrouk et al. in which 65-year-old men were invited to an abdominal aortic aneurysm screening program and those with lower socioeconomic status showed lower

participation (144). By adding new screening sites in the STROKESTOP II study in deprived areas, we observed a markedly increased participation in population groups with low socioeconomic status. These results reinforce the importance of geographic proximity in screening, especially for those of lower socioeconomic status. A recent systematic review found that individuals with lower socioeconomic status showed poorer outcomes when AF was present (23), which is an important reason to attempt to lower the socioeconomic gradient in AF screening. A systematic review found that barriers and facilitators to participation in health checks for cardiometabolic disease were heterogenous, which makes it difficult to develop a "one size fits all" approach for increased uptake (145).

In study IV a detailed description of non-participants found that they were generally in poorer health, had lower socioeconomic status and were not as mobile. They had spent more days in hospital both during the last year as well as during the last five years, a sign of more morbidities and frailty. The CHA_2DS_2-VASc score was higher among non-participants, highlighting that these are the individuals at high risk for stroke if diagnosed with new AF. The gradient of the CHA_2DS_2-VASc score ranging from significantly higher in the Q1 to lower in Q4 could be interpreted as a proxy that the screening benefit would be largest in the group least likely to attend.

In the non-participants group a larger proportion of previously known AF was found than in the participants group. Possibly indicating that individuals with a prior diagnosis of AF would not see the point in attending an AF screening study. On the other hand, it could also be result of these individuals having been in contact with the healthcare system because of other morbidities and thereby having been diagnosed with AF. The difference in untreated AF between participants and non-participants, where non-participants had a higher proportion of untreated AF, was largest in the group with CHA_2DS_2-VASc scores 2, which could possibly be a sign of those individuals being healthier and not having had contact with the healthcare system resulting in subclinical AF no being identified.

Interestingly, the overlapping of characteristics in both participants and non-participants unveils that no single factor is the reason of non-attendance. Although the difference between the groups was significant in most categories, there were still individuals that attended the screening with dementia, Parkinson's disease, alcohol problems to name a few, which we would have expected would possibly deter participation altogether.

The number of non-participants that had been hospitalised gives way to further explorations of systematic AF screening within the in-hospital setting to identify high-risk and frail patients with new AF. A Belgian study where older adults were

screened for AF in a geriatric ward in a hospital setting demonstrated the feasibility of this approach and identified a significant number of patients with new AF (140). We found no difference in number of outpatient visits in the two groups, possibly highlighting that inpatient care is a strong sign of frailty and morbidity whereas outpatient visits could be a way of primary prevention.

7.8 LIMITATIONS

Systematic screening is a costly public health intervention thus there needs to be enough scientific evidence that it is of greater good for public health and society. Luckily, several large-scale, randomised, controlled systematic screening studies are ongoing that aim to answer the question if screening indeed does reduce stroke and/or death, the STROKESTOP trials being among them.

In this thesis the study population was 75/76-year-olds in the Stockholm region. That fact is important when considering the external validity of the studies and how the results can be applied to other populations. However, this age group has been found to be optimal in simulation studies for AF screening (71) and the setting of the screening, with invitation by mail and lack of exclusion criteria could possibly be the scenario of a future real-life screening program. The participants in STROKESTOP II were found to be healthier than the non-participants which has to be considered when applying these results to other populations.

In study I the participation was slightly lower than expected, and the participants had moderate mean CHA_2DS_2-VASc score, suggesting that the ones attending the screening might have been healthier than the non-participants. That indication was confirmed in Study IV. Medical history in study I was self-reported without confirmation from medical records, which could have affected validity of medical history data. As for the predictors for AF in our multivariable analysis, we were restricted to the variables collected within the trial so there is always risk for unknown residual confounding. As for the AF diagnosis in this study, the low-risk group only performed one single-lead ECG at the screening visit, so AF could be underdiagnosed in this group. The hypothesis, however, is that individuals in the group with low NT-proBNP have a lower risk for both incident AF as well as stroke, something that will be evaluated in our final analysis of the STROKESTOP II study in a five years' time.

Study II is a diagnostic accuracy study on pulse palpation compared to single-lead ECG. The gold standard of rhythm interpretation is considered to be a 12-lead ECG, but we did not perform 12-lead ECGs on all participants in this study. The 2020 ESC AF Guidelines recommend 30-second rhythm strip for diagnosing AF, and a 12-lead

ECG is not needed to confirm that diagnosis. The aim of this study was to diagnose AF rhythm and no other specific arrhythmia. Single-lead ECGs can be difficult to interpret if the signal quality, which necessitates a 12-lead ECG, is poor.

Participants were not asked to specify their palpitation symptoms any further than to answer a simple yes/no question making it only possible to infer on history of palpitations.

Pulse palpation was performed by trained healthcare professionals after instructions, which could have increased the accuracy of pulse palpation. There might be observer variability as the subjective element cannot be excluded from pulse palpation. Although care was taken to ensure that pulse palpitation was performed without results of the single-lead ECG, there is a possibility of reviewer bias after the single-lead ECG or clinical review bias as the patients reported their medical history. We did not evaluate the intra- or interobserver variability of the cardiologists studying the 12-lead ECGs in the study.

The intrinsic factors of a diagnostic test (sensitivity and specificity) do not depend on disease prevalence, but the predictive values are strongly dependent on disease prevalence. AF prevalence in this cohort was 0.5%, and the negative predictive value becomes very high due to that fact. This this has to be taken into account when applying these results to other populations.

In Study III data on participants from the STROKESTOP I and STROKESTOP II studies were collected a few years apart, and the demographics of the areas compared may have changed in between the data withdrawal. This may have possibly introduced misclassification bias. In the STROKESTOP II study there was a lower proportion of individuals in the lowest income category compared to the STROKESTOP I study. This may have introduced a bias where we would detect a difference because of demographics rather than participation rate.

The changes (website, more languages in the patient information, more sites) made to increase the screening uptake cannot be separated, hence which had the strongest impact is a question this study cannot answer. This feature may decrease the external validity of this study.

In Study IV 75/76-year-olds in the Stockholm region were studied. This has to be considered when applying the results to other groups or other settings. While the analyses included rich information on medical history, pharmaceutical dispensations and socioeconomic status, there may be other factors that predict screening participation that we were unable to measure. In addition, while the registers we relied on are considered to be of high quality (146, 147) we cannot rule out measurement errors such as missing or misclassified diagnoses. The healthcare registers

in Sweden collect prospectively data covering the entire public hospital-associated health care system in Sweden. This is beneficial for external validity, particularly for countries with similar patient compositions and health care systems, but as we did not have information on private health care and primary health, the data set may have some gaps.

8 CONCLUSIONS

Using NT-proBNP in a stepwise, systematic AF screening study yielded a large proportion of new AF cases (4.4%) in the group with elevated NT-proBNP, increasing the prevalence in participants by almost one third. NT-proBNP was the strongest predictor of new AF. OAC treatment was well accepted in the group diagnosed with new AF and compliance to the treatment at one-year follow-up was high.

Pulse palpation was inferior to single-lead ECG when screening for AF. We would advocate using a single-lead ECG, from which the diagnosis of AF can be made simultaneously rather than the triage test of pulse palpation. History of palpitations did not predict new AF during this single-time point screening.

Decentralisation of screening sites had a positive impact on screening participation. The positive effect was found not only in the groups already with higher odds of attending, but also in the groups of lower socioeconomic status who have lower odds of attending. This indicates that bringing the screening closer to neighbourhoods with lower socioeconomic status lowers the socioeconomic gradient often seen in screening.

The potential yield of untreated atrial fibrillation was higher among non-participants in the STROKESTOP II study than among those that participated. Non-participants were of poorer health, had lower socioeconomic status and were less mobile than participants. They also had higher CHA_2DS_2-VASc scores, highlighting their high stroke-risk and probable gain from attending screening.

9 CLINICAL IMPLICATIONS

Whether or not NT-proBNP can be used as an aid to decide whom to screen for AF and whether it is cost-effective for society, are questions we as of yet do not have the answers to but hope to have in a few years' time. What we did find in study I was that NT-proBNP was the strongest factor predicting new AF in a multivariable analysis and a 50% higher proportion of individuals were diagnosed with AF in the high-risk group in STROKESTOP II than were found in the whole group in the STROKESTOP I study. In a sub-study to the STROKESTOP II study in participants with NT-proBNP >900ng/L, 30% of the patients were diagnosed with new AF. Our results support the use of NT-proBNP and highlight its probably discriminative value in AF screening. In patients with NT-proBNP >125ng/L and even more so in those with NT-proBNP>900ng/L one should consider screening for AF.

Pulse palpation is recommended according to the ESC AF Guidelines, but our results strengthen the case for more sensitive diagnostic tools for screening than pulse palpation. With today's technological advances there are abundant, easy-to-use modalities that can diagnose AF directly and save clinicians and individuals from many false positive results of the pulse palpation test.

Adding screening sites or in some way bringing the screening closer to more socioeconomically deprived areas would increase participation in these areas and, in that way, hopefully decrease the socioeconomic gradient that is found in many screening programs.

Studying both socioeconomic- and health factors in non-participants we found that low income and hospitalisations had the strongest negative influence on participation. In planning future screening scenarios focus should be put on how to reach those less likely to attend as they would benefit from the screening efforts e.g. by bringing the screening closer to low-income areas as well as possibly designing active screening in hospital environments.

10 FUTURE PERSPECTIVE

Screening is a complex battery and so is AF so how to design an ideal screening program is obviously a very difficult question, possibly without one right answer. How societies around the world should design a screening program can vary because of different healthcare systems and priorities.

In study I, NT-proBNP was used to try to identify high-risk individuals for incident AF. We found 50% more new AF cases in the high-risk group in the STROKESTOP II trial compared to the STROKESTOP I trial, in which all individuals underwent prolonged screening. This was in accordance with the expected yield of new AF in the high-risk group. NT-proBNP is associated with incident AF and finding the right biomarker, possibly one for finding AF and another one to predict which individuals have higher risk of suffering complications from OAC treatment is something that could be studied to better control and personalise treatment.

Technological advances have been accelerating over the last decade and new modalities for detecting AF will probably be seeing the light of day in the next years. Which modality is optimal to screen for AF is sure to be the research object of many studies to come.

By increasing the screening sites, individuals already more likely to attend screening reacted with increased participation. For the screening not to be a way of increasing inequality even more we need to focus on reaching those in more socioeconomically deprived areas and those that would benefit from screening. This could possibly be done by placing screening sites in socioeconomically deprived areas, possibly using general practices, hospitals or by using mobile screening clinics.

In study IV we found that participation was worse in low-income, high-risk and hospitalised individuals. The results from study IV could potentially help when designing future screening programs or future screening studies. Focus should be put on how to include those with lower income and studies could try to find what factors can have a positive effect on individuals in low-income groups. It would also be interesting to study systematic screening in hospitalised patients, as a way of reaching those with many risk factors and at the same time include those that have more difficulty attending screening.

11 SVENSK SAMMANFATTNING

11.1 BAKGRUND

Kardiovaskulära sjukdomar är den vanligaste dödsorsaken i världen från 15 års ålder och uppåt. Där spelar förmaksflimmer en stor roll som den vanligaste kliniska hjärtarytmin som påverkar över 33 miljoner människor i världen. Förmaksflimmer är en ledande orsak till sjuklighet och död, där hjärtsvikt, stroke och död är de mest befarade komplikationerna. Förmaksflimmer är en betydelsefull orsak till stroke men den risken kan minskas med åtminstone två-tredjedelar hos högriskpatienter genom att starta blodförtunnande behandling. Förmaksflimmer behöver inte ge symptom och-särskilt äldre individer-kan vara drabbade av förmaksflimmer utan att veta om det eller känna av det. Eftersom förmaksflimmer är ett vanligt och för de allra flesta ett kroniskt problem, spås bli ännu mer utbrett inom närmaste 50 åren och det finns en effektiv behandling verkar det uppfylla World Health Organisations kriterier för populationsscreening. Att screena för förmaksflimmer och sätta in blodförtunnande behandling när det är indicerat skulle kunna förhindra stroke och lidande för många. Om screening för förmaksflimmer minskar risken för stroke och samtidigt är kostnadseffektivt ur ett samhälleligt perspektiv är ännu en fråga utan svar. Tills dess pågår forskning för att försöka hitta den optimala screeningmetoden, vilket är bakgrunden till STROKESTOP I och STROKESTOP II studierna.

11.2 SYFTE

Första delstudien syftar till att studera antal deltagare i STROKESTOP II studien som fick förmaksflimmerdiagnos efter att de sorterades i högrisk eller lågriskgrupper beroende på NT-proBNP värde. Vi studerade även hur stor andel av de som diagnosticerades med förmaksflimmer blev insatta på blodförtunnande behandling och i hur stor utsträckning de fortfarande stod på behandlingen efter 1 år.

I andra delstudien jämförde vi metoderna pulspalpation och enavlednings-EKG vid förmaksflimmerscreening och även om man hittar mer förmaksflimmer vid screening hos individer som har känt av hjärtklappning än de som inte har känt det.

I tredje delstudien analyserade vi sociodemografiska skillnader i deltagandet i STROKESTOP II studien samt jämförde resultaten mellan STROKESTOP I och STROKESTOP II studierna efter tillägg av två nya screening-mottagningar i STROKESTOP II.

I fjärde delstudien jämförde vi deltagare och icke-deltagare avseende socioekonomisk status och hälsostatus och estimerade potentiell fångst av obehandlat förmaksflimmer inom icke-deltagargruppen.

11.3 METODER

I delstudie I blev alla 75/76 åringar i Stockholm randomiserade 1:1 till interventionsgrupp eller kontrollgrupp. Individer i interventionsgruppen blev inbjudna att delta i förmaksflimmerscreening studien STROKESTOP II. Deltagare utan tidigare känt förmaksflimmer gjorde blodprov där man analyserade biomarkören NT-proBNP och delade deltagarna i en högriskgrupp eller en lågriskgrupp beroende på NT-proBNP nivå. De som hade NT-proBNP <125ng/L blev kategoriserade som lågriskgrupp och de med NT-proBNP≥125 ng/L blev kategoriserade till högriskgruppen. Alla gjorde enavlednings-EKG vid screeningbesöket medan högriskgruppen blev ombedda att göra förlängd screening och göra enavlednings-EKG mätningar fyra gånger dagligen under två veckors tid. Om förmaksflimmer diagnosticerades blev deltagarna remitterade till en kardiolog för bedömning och för att sätta in behandling om indikation fanns för blodförtunnande läkemedel.

I delstudie II blev alla deltagare i STROKESTOP II studien som inte hade sedan tidigare känt förmaksflimmer inkluderade. Sjuksköterskor och undersköterskor tog på screeningbesöket först radialis-pulsen hos deltagarna och registrerade om den var regelbunden eller oregelbunden. Därefter fick deltagarna göra ett enavlednings-EKG som registrerades som sinusrytm eller förmaksflimmer. Deltagarna svarade på frågan ”har du känt av hjärtklappning” med ja eller nej.

I delstudie III blev alla som blev inbjudna att delta i STROKESTOP II inkluderade och samma datavariabler från STROKESTOP I deltagare var redan samlade. I STROKESTOP II studien infördes två ytterligare screening-mottagningar i de områden där man såg lägst deltagande i STROKESTOP I. Hos deltagare tog man sjukdomsanamnes, tog blodprov och enavlednings-EKG vid screeningbesöket. Information om de distrikt som alla inbjudna tillhörde användes för så kallad geo-mapping analys med hierarkisk Bayes metod för att studera skillnaderna i deltagande. Individdata på de socioekonomiska variablerna utbildningsnivå, inkomst, invandringsstatus samt civilstånd samlades anonymiserad för deltagare samt icke-deltagare från SCB.

I delstudie IV använde vi registerdata från Patientregistret, läkemedelsregistret och Statistikmyndigheten för att jämföra deltagare och icke-deltagare avseende socioekonomiska och hälsodata. En random forest-modell tränades för att skatta sannolikheten för screeningdeltagande baserat på information om sociodemografi och sjukdoms- och läkemedelshistorik. De skattade sannolikheterna användes sedan för att skatta potentiellt screeningutbyte hos icke-deltagare.

11.4 RESULTAT

I STROKESTOP II studien deltog 6868 individer och 6315 (91,9%) deltagare var utan tidigare känt förmaksflimmer. Av deltagarna utan känt förmaksflimmer hade 3766/6315 (59,6%) NT-proBNP≥125 ng/L och gick vidare med två veckors intermittenta enavlednings-EKG mätningar fyra gånger dagligen. Nytt förmaksflimmer hittades hos 4,4% (95% CI 3,7–5,1) av deltagarna som kategoriserades till högriskgruppen. Hos alla deltagare utan tidigare känt förmaksflimmer hittades således nytt förmaksflimmer hos 2,6% (95% CI 2,2–3,0) genom screening. Förekomsten av känt förmaksflimmer ökade från 8,1% i deltagargruppen till 10,5% genom screening, en ökning på 30%. Hos de med nytt förmaksflimmer blev blodförtunnande behandling insatt hos 94,5% efter bedömning hos kardiolog och 96% av dessa hade kvar blodförtunnande behandlingen vid ettårsuppföljning.

I delstudie II blev 6159 deltagare inkluderade, varav 461 hade oregelbunden puls (7,5%). Av dessa hade 22 (4,8%) förmaksflimmer på enavlednings-EKG. Av de deltagare som bedömdes ha regelbunden puls hade 6 (0,1%) förmaksflimmer på enavlednings-EKG. Sensitiviteten av pulspalpation var 78,6% och positivt prediktivt värde 4,8%. Andelen deltagare med nytt förmaksflimmer var inte signifikant högre hos de som hade uppgivit att de känt av hjärtklappning.

I delstudie III var deltagandet i STROKESTOP II högre hos de med hög utbildning, hög inkomst, icke-invandrare samt gifta individer. Deltagandet jämfört mellan STROKESTOP I och STROKESTOP II ökade signifikant, inom alla socioekonomiska variabler, kring de nya screening-mottagningarna.

I delstudie IV var prevalensen av tidigare förmaksflimmer 17.9% hos icke-deltagare jämfört med 8.9% hos deltagare. De viktigaste faktorerna som förutspådde icke-deltagande var låg inkomst, sjukhusvistelse samt högre CHA_2DS_2-VASc poäng. Estimerat utbyte av obehandlat förmaksflimmer var högre bland icke-deltagare än deltagare.

11.5 SLUTSATSER

I en systematisk screening-studie för förmaksflimmer stratifierad för NT-proBNP, diagnosticerades 4,4% av deltagarna i högriskgruppen (NT-proBNP≥125 ng/L) med förmaksflimmer. Blodförtunnande behandling accepterades väl hos de med nytt förmaksflimmer.

Puls palpation hade sämre diagnostiska prestanda jämfört med enavlednings-EKG för att diagnosticera förmaksflimmer och vi rekommenderar enavldenings-EKG framför pulspalpation för screening av förmaksflimmer. Hjärtklappning var inte associerad med nytillkommet förmaksflimmer.

Decentralisering av screeningplatserna i STROKESTOP II hade en signifikant positiv verkan på deltagandet. Att öppna screeningplatser där man tidigare såg sämre deltagande hade en positiv inverkan på deltagandet genom alla delar av socioekonomiska nivå.

Potentiellt utbyte av obehandlat förmaksflimmer var högre bland icke-deltagare än deltagare. Icke-deltagare hade högre CHA_2DS_2-VASc poäng som understryker att de har hög strokerisk och skulle kunna gynnas av förmaksflimmerscreening.

12 ÍSLENSK SAMANTEKT

12.1 INNGANGUR

Hjarta og æðasjúkdómar eru algengasta dánarorsök hjá einstaklingum eldri en 15 ára. Gáttatif sem algengasta klíníska hjartsláttaróreglan spilar þar stóran sess en það er áætlað að rúmlega 33 miljónir manns séu með gáttatif í heiminum. Gáttatif getur meðal annars aukið líkur á hjartabilun, heilaslagi og dauða. Það er vel þekkt að gáttatif auki hættuna á heilaslagi, en þá áhættu er hægt að minnka um tvo þriðju með blóðþynnandi meðferð hjá þeim sem eru í áhættuhóp. Gáttatif getur verið nánast eða alveg einkennalaust, sérstaklega hjá eldri einstaklingum og er þar af leiðandi vangreint í þeim hópi. Gáttatif uppfyllir viðmið World Health Organization (WHO) um samfélagslega skimun þar sem það er algengur sjúkdómur, verður langvinnt vandamál hjá flestum sjúklingum, það er til meðferð, og spár segja til um að tíðnin muni aukast á næstu fimmtíu árum. Hvort að samfélagsleg skimun fyrir gáttatifi lækki tíðni heilaslaga og minnki þannig bæði þjáningar einstaklinga og borgi sig fyrir samfélagið í heild er spurning sem við vitum ekki ennþá svarið við en STROKESTOP I og STROKESTOP II rannsóknirnar leitast við að svara þeirri spurningu

12.2 MARKMIÐ

Í fyrstu rannsókn þessarar doktorsritgerðar var markmiðið að rannsaka hlutfall þátttakenda í STROKESTOP II sem hlutu greininguna gáttatif eftir að hafa verið flokkaðir í áhættuhóp eða ekki áhættuhóp samkvæmt niðurstöðu úr blóðprófi þar sem mælt var lífmerkið NT-proBNP. Við rannsökuðum einnig hversu stórt hlutfall þeirra sem greindust með gáttatif byrjuðu á blóðþynnandi meðferð og hversu stórt hlutfall var ennþá á blóðþynnandi meðferð að ári liðnu.

Í annarri rannsókn bárum við saman tvær skimunaraðferðir, annars vegar að þreifa púls á úlnlið til að greina óreglulegan hjartslátt og hins vegar einnar leiðslu hjartalínurit. Við skoðuðum einnig hvort að þeir sem höfðu fundið fyrir hjartsláttareinkennum voru líklegri til að greinast með gáttatif við skimun.

Í þriðju rannsókn bárum við saman félagsfræðilegan mun á þeim sem tóku þátt í STROKESTOP II og þeim sem ekki tóku þátt og bárum einnig saman STROKESTOP I rannsóknina og STROKESTOP II rannsóknina eftir að hafa bætt við tveim skimunarstöðvum í STROKESTOP II.

Í fjórðu rannsókn bárum við saman félagfræðilega og heilsufarslega þætti þátttakenda og þeirra sem ekki tóku þátt í STROKESTOP II. Við áætluðum einnig mögulegt hlutfall þeirra með meðhöndlanlegt gáttatif í þeim sem ekki tóku þátt í rannsókninni.

12.3 AÐFERÐIR

Í fyrstu rannókninni voru allir íbúar í Stokkhólmi fæddir 1940 og 1941 slembiraðaðir 1:1 til að vera boðin þáttaka í STROKESTOP II eða vera viðmiðunarhópur. Hjá þeim sem tóku þátt í rannsókninni og ekki voru með þekkt gáttatif var tekið blóðpróf þar sem lífmerkið NT-proBNP var mælt. Svo var þeim skipt í tvo hópa, þar sem annar hópurinn var skilgreindur sem áhættuhópur ef NT-proBNP ≥125 ng/L. Allir þáttakendur sem ekki höfðu þekkt gáttatif fengu að taka einnar leiðslu hjartalínurit í skimunarheimsókninni. Þeir þátttakendur sem tilheyrðu áhættuhópnum tóku svo með sér einnar leiðslu hjartalínuritið heim og voru beiðnir að taka með því hjartalínurit fjórum sinnum á dag í þrjátíu sekúndur í senn næstu tvær vikurnar. Ef gáttatif greindist voru þátttakendurnir sendir til hjartalæknis til mats og sett inn blóðþynningarlyf ef ekki voru frábendingar fyrir því.

Í rannsókn tvö tóku þáttakendur í STROKESTOP II sem ekki höfðu þekkt gáttatif þátt. Hjúkrunarfræðingar og sjúkraliðar sem unnu við skimunina þreifuðu fyrst úlnliðspúlsinn á einstaklingunum í 30 sekúndur og skráðu hann sem reglulegan eða óreglulegan. Svo fengu þáttakendurnir að taka einnar leiðslu hjartalínurit og það var skráð sem sinus taktur eða gáttatif. Þáttakendurnir svöruðu einnig spurningunni „hefur þú fundið fyrir hjartsláttaróþægindum?“ með já eða nei.

Í þriðju rannsókninni skoðuðum við alla sem hafði verið boðið að taka þátt í STROKESTOP II með tilliti til félagsfræðilegu þáttanna: menntunarstig, tekna, innflytjendastöðu og hjúskaparstöðu. Við höfðum þegar upplýsingar um um þessa þætti hjá þeim sem hafði verið boðið að taka þátt í STROKESTOP I. Í STROKESTOP II hafði tveim skimunarstöðvum verið bætt við frá því í STROKESTOP I, þar sem mælst hafði lægst þáttaka. Upplýsingar um sóknir allra sem var boðið voru notaðar til að búa til kort fyrir svokallaða „Geo-mapping“ greiningu samkvæmt stigveldi Bayes aðferð til að sýna muninn á þáttökunni.

Í fjórðu greininni bárum við saman félagsfræðilega þætti og heilsufarslega þætti hjá þátttakendum og þeim sem ekki tóku þátt en upplýsingar um það fengust hjá Sænskum skrám sem halda utan um þessar upplýsingar. Svokallað „random forest“ var þjálfað til að áætla stig fyrir tilhneigingu einstaklinga til að taka þátt. Þessi stig voru svo notuð til að áætla mögulegt hlutfall sjúkdóms hjá þeim sem ekki tóku þátt.

12.4 NIÐUSTÖÐUR

Alls svöruðu 6868 einstaklingar boðinu um að taka þátt í STROKESTOP II rannsókninni. 6315 (91,9%) af þeim reyndust ekki með þekkt gattatif. Hjá 3766 (59,6%) einstaklingum mældist NT-proBNP gildi yfir 125ng/L og voru þeir einstaklingar skilgreindir sem áhættuhópur og beðnir um að taka einnar leiðslu hjar-

talínurit fjórum sinnum á dag í tvær vikur. Í áhættuhópnum greindust 4,4% (95% CI 3,7–5,1) af einstaklingunum með nýtt gáttatif. Einn greindist með gáttatif við skimunarskoðunina í hópnum sem ekki var talinn áhættuhópur. Samanlagt greindust því 2,6% (95% CI 2,2–3,0) af öllum hópnum sem ekki hafði þekkt gáttatif með nýtt gáttatif við skimun. Algengi gáttatif jókst þar af leiðandi frá 8,1% í 10,5% hjá öllum þátttakendum sem er 30% aukning. NT-proBNP var sterkasti forspárþátturinn fyrir nýju gáttatifi í fjölbreytugreiningu hjá áhættuhópnum. Einstaklingar sem greindust með gáttatif hittu hjartalækni til mats og 94,5% fengu fyrirbyggjandi blóðþynnandi meðferð. Af þeim voru 96% ennþá á blóðþynnandi lyfjum að ári liðnu.

Í rannsókn tvö voru 6159 þáttakendur og þreifaðist óreglulegur púls hjá 461 (7,5%). Af þeim greindust 22 (4,8%) með gáttatif á einnar leiðslu hjartalínuriti. Hjá þeim þáttakendum þar sem púlsinn var reglulegur greindust 6 (0,1%) manns með gáttatif. Næmni púlstökunnar var 78,6% og jákvætt forspárgildi var 4,8%. Hlutfall þátttakenda sem sögðust hafa fundið fyrir hjartsláttaróþægindum var ekki hærra meðal þeirra sem greindust með gáttatif.

Í þriðju rannsókninni sást betri þátttaka hjá einstaklingum sem voru með meiri menntun, hærri laun, hjá giftum einstaklingum og þeim sem ekki voru innflytjendur. Þátttakan jókst, innan allra félagsfræðilegra breyta, í nánd við nýju skimunarstöðvarnar.

Í fjórðu rannsókninni voru 17.9% af þeim sem ekki mættu með áður þekkt gáttatif borið saman við 8.9% af þeim sem tóku þátt. Mikilvægustu þættirnir sem höfðu áhrif á þátttökuna voru lág laun, sjúkrahúsinnlagning og fleiri CHA_2DS_2-VASc stig. Áætlað ómeðhöndlað gáttatif var hærra (3,6%) meðal þeirra sem ekki tóku þátt en meðal þeirra sem tóku þátt (3,3%).

12.5 ÁLYKTANIR

Í NT-proBNP lagskiptri skimun fyrir gáttatifi, greindust 4,4% af þáttakendunum í áhættuhópnum með nýtt gáttatif. Blóðþynnandi meðferð var sett inn hjá langflestum þeirra sem greindust með nýtt gáttatif og voru þeir ennþá á meðferð að ári liðnu.

Þreifing á púls er síðri leið til að greina gáttatif en einnar leiðslu hjartalínurit og við mælum með því að notast frekar við einnar leiðslu hjartalínurit við skimun fyrir gáttatifi. Hjartsláttaróþægindi hafa ekki forspárgildi fyrir greiningu gáttatifs við skimun.

Dreifing skimunarstaðanna hafði jákvæð áhrif á þáttöku og það að oppna skimunarstaði á svæðum þar sem áður var verri þátttaka hafði jákvæð áhrif á þátttöku meðal allra félagsfræðilegu breytna sem metnar voru.

Áætlað hlutfall ómeðhöndlaðs gáttatifs var hærra meðal þeirra sem ekki tóku þátt í STROKESTOP II en þeirra sem tóku þátt. Þeir sem ekki tóku þá voru með fleiri

CHA_2DS_2-VASc stig, sem bendir til þess að þeir séu með aukna áhættu á heilaslagi og myndu hagnast á að mæta í skimun.

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