Atrial fibrillation: Epidemiology and screening at 65 years

Design and cross-sectional analysis of the Akershus Cardiac Examination (ACE) 1950 Study cohort

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A dissertation for the degree of PhD

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"In theory, screening is an admirable method of combating disease... [but] in practice, there are snags"

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Preface

In 2011-2012, my supervisors and I designed a study to investigate the epidemiology of atrial fibrillation in a cohort drawn from the general population aged 65 years. The study was supposed to be simple and effective to perform, focusing on variables relevant to atrial fibrillation. My role was to coordinate design, planning and implementation of the study, which we named *Atrial Fibrillation in Akershus (AFIA)*.

However, as plans became known among fellow researchers at our institutions, it drew attention, not only to its potential to investigate atrial fibrillation, but also related disorders. Hence the focus was widened significantly, and my task as a study coordinator grew accordingly.

During the following years, I experienced the fearful joy to design and carry out a large cohort study, the *Akershus Cardiac Examination (ACE) 1950 study*, together with the rest of the Steering Committee. The role as study coordinator included development of case record forms, questionnaires, procedures and other ‘tools’ to be used in the implementation of the study, and to coordinate and take part in the team performing the baseline visits of the *ACE 1950 study*.

Hence, my work as a PhD fellow reached further than the papers and results reported in this thesis.
Acknowledgements

A true team effort between Bærum Hospital, Akershus University Hospital and 3706 volunteer women and men born in 1950 is the foundation of the Akershus Cardiac Examination (ACE) 1950 study.

My main supervisor Arnjot Tveit came up with the initial idea to the study, along with my co-supervisor, Pål Smith. Arnjot Tveit is the head of the Department of Medical Research at Bærum Hospital and has been the Principal Investigator of the ACE 1950 study from the start. He gave me the opportunity to actively take part in the initial planning of the ACE 1950 study. As my supervisor he showed me a great deal of trust and taught me how to work patiently without hasted decisions. I appreciate your friendliness, calmness, unpretentiousness and your fine balance between guiding and pushing me in the right direction.

I am also grateful to my co-supervisor Pål Smith, particularly in the process of writing. He also actively took part in the screening sub-study, performing study visits, ECG analyses, and validation of atrial fibrillation diagnoses.

Mona Olufsen and Steve Enger deserve a wholehearted thanks, following me from day 1, supporting me with patience and humour since the very start. Your attention to details, logistics and methodology has been invaluable to me, and to the study.

Sophia Onarheim has been all-important in reading (tens of) thousands of ECGs and taking care of participants and study logistics, particularly in the screening sub-study. Jon Brynildsen and Hege K. N. Larsen did the same great job at Akershus University Hospital, along with Pål Smith, in a remarkably short time.

My sincere gratitude goes to all my fellow ACE 1950 PhD colleagues at Bærum Hospital and Akershus University Hospital. A special thanks to Håkon Ihle-Hansen for close collaboration, and the invaluable job of keeping the baseline examinations at Bærum Hospital going during my long parental leave; you are hard-working and always focused on getting tasks done.

To all the rest of my colleagues at the Department of Medical Research: Hilde Larhammer and Vigdis B. Semb were crucial in performing the baseline examinations at Bærum Hospital from the very start, along with Kristine G. Haider, joining later. Sara R. Ulimoen, Anne Pernille Ofstad and Hege Ihle Hansen were important as the ‘senior PhD students’ when I first started. Likewise, Ingrid E. Christophersen, you have been a great asset to me and the project throughout the period. Anja W. Horjen, you have been of invaluable support, particularly during the last phase of writing this thesis. Thanks also to our statistician Ståle Nygård for his support and advice. To all the rest in the Heart & Brain Research Group; Marius Myrstad, Marie Ursin, Guri Hagberg, Sigrun L. Eskeland, Katrine Enge, Silje M. Kalstø, Elizabeth L. Andersen, Kristine S. Folkenborg, Magnar G. Solberg and Peter S. Rønningen – thank you all.

The Department of Medical Research at Bærum Hospital has a unique research milieu and has been a great workplace through these years. Good colleagues in a very sociable and supportive working environment have been important to me. Some of my best memories are from our congress trips around Europe, christmas parties, or during the daily coffee and lunch breaks.
Next, I also want to express my profound gratitude to Helge Røsjø (ACE 1950 Co-Principal Investigator, Akershus University Hospital), Magnus N. Lyngbakken and the rest of the ACE 1950 steering committee, Torbjørn Omland, Kjetil Steine (as well as Pål Smith and Arnjot Tveit) for your involvement – all of you have been extremely important in carrying this study through. A number of other colleagues and research staff in the Cardiothoracic Research Group at Akershus University Hospital have contributed immensely towards the same, and completed a large number of examinations in impressively short time: Thea Vigen, Vigdis Bakkelund, Annika Lorentzen, Marit Holmejord Pedersen, Zarina Aslam, Silje M. Kalstø, Angelica Marianne Berg, Peder Myhre, Nina Faksvåg Caspersen, Gunnar Einvik, Vidar Søyseth, Anupam Chandra, Dag Aarsland, Bente Thommessen, Ole Morten Rønning – and many more.

The ACE 1950 ‘echo team’ has been great, introducing me to the field of echocardiography recording and analysis. Thanks to Eivind B. Orstad, Steve Enger, Erika N. Aagaard, Brede A. Kvisvik, Mohammad Osman Pervez, and our echo supervisor Kjetil Steine.

A number of research assistants have contributed towards data collection, handling and validation of data. A special thanks to Gaute R. Jenssen, who was heavily involved in the screening sub-study.

Inger Ariansen, an atrial fibrillation researcher and epidemiologist at the Norwegian Institute of Public Health; you have been of great support during my work; always helpful, friendly and enthusiastic.

The ACE 1950 study would not have been possible without financial support from the two main institutions; Bærum Hospital (Vestre Viken Hospital Trust) and Akershus University Hospital. I am also grateful to the Dep. of Medicine at Bærum Hospital, providing flexibility by letting me work half-time in the clinic during periods of my research.

Thanks also to the Faculty of Medicine at University of Oslo for the formal part of my PhD education, and to all three members of the doctoral thesis evaluation committee; Mårten Rosenqvist, Bente Morseth and Waleed Ghanima.

Nasjonalforeningen for folkehelsen, a non-governmental organisation promoting cardiovascular research, supported me with a PhD scholarship. The staff and volunteers in the organisation have shown great enthusiasm and interest in our work. Venner av Bærum sykehus, the patients’ interest organisation at Bærum Hospital, also deserves recognition for their interest in the project and their substantial funding for one of the cardiovascular ultrasound machines used in the study.

And – thanks to my friends, particularly those of you who are not (at all) so interested in atrial fibrillation or medicine. Perspectives beyond that have (hopefully) prevented me from too much narrow-mindedness.

Last, but by no means least, my deepest thanks to all of my family, but most of all to Synne, supporting me in all possible ways – but also reminding me of the value of maintaining both a family life and an intellectual life, outside medicine. And finally, thanks to our three lovely children; Solveig (8), Thorvald (5) and Alfred (2). You remind me, every day, of life outside work and research.

Trygve Berge

Bærum/Oslo, Norway, March 2019
Summary

BACKGROUND: Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting >5% after the age of 65 years. In Norway, there are few studies on AF prevalence. AF is an important risk factor for ischemic stroke, and the risk is amplified by aging and cardiovascular comorbidities. AF is often paroxysmal and/or asymptomatic. Thus, it can remain undiagnosed until discovered incidentally, or when a stroke occurs. For this reason, screening has been suggested to reveal unknown AF, with the purpose of offering stroke prevention by anticoagulant treatment.

AIMS: To design a cardiovascular cohort study suitable to investigate development and progression of AF and related cardiovascular diseases, and to perform baseline examinations (Paper I). In this cohort, at the age of 63-65 years, we investigated the prevalence of AF and associated cardiovascular risk factors (Paper II). We also aimed to assess the yield of systematic screening for unknown AF by two-week intermittent, handheld electrocardiography (ECG) in individuals aged 65 years with additional risk factors for stroke (Paper III).

METHODS: All women and men born in 1950 and resident in Akershus county, Norway (n=5,827) were invited to the Akershus Cardiac Examination (ACE) 1950 study. The baseline examination was planned as a comprehensive cardiovascular examination, including 12-lead ECG, ultrasound imaging and biobanking (Paper I). In a cross-sectional analysis, we reported prevalence of AF, other cardiovascular diseases and associated risk factors. All self-reported and newly detected AF diagnoses were validated (Paper II). At the age of 65 years, cohort participants without a history of AF, and with at least one additional risk factor for stroke, other than age or sex (CHA_2DS2-VASc score ≥2 for men or ≥3 for women), were invited for a two-week screening by intermittent, handheld ECG (‘thumb ECG’), twice daily (Paper III).

RESULTS: An age cohort of 3,706 individuals (63.6% participation rate; 48.8% women) was established (Paper I). Mean age at enrolment was 63.9±0.7 years. Prevalence of validated AF was 4.5%, including AF detected at baseline in 0.3%. AF individuals, among both sexes, were taller, heavier and had more cardiovascular comorbidity compared to the rest of the cohort. A family history of AF was more frequently reported among women with AF, compared to men with AF (Paper II). Among 65-year-olds at increased risk of stroke, screening for AF identified 0.9% unknown AF. Apart from a higher proportion of diabetes, risk factors and characteristics among individuals with screen-detected AF were comparable to that of known AF. The total prevalence of AF, after screening, among all 65-year-olds with at least one additional risk factor for stroke, was 7.6% (paper III).

CONCLUSIONS: The ACE 1950 study population may serve as basis for important follow-up studies. We identified a higher prevalence of known AF than previously reported in this age group. The study was the first to model a potential systematic screening for AF in a general population at the age of 65 years. In addition to a diagnostic yield of ~1% screen-detected AF, we demonstrated the practical use of handheld ECG for this purpose.
List of scientific papers

The thesis is based on the following three scientific papers, referred to by their Roman numeral throughout the thesis:


Heart and Brain Interactions – the Akershus Cardiac Examination (ACE) 1950 Study Design


Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65 years old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study

BMJ Open 2018; 8: e021704. DOI: 10.1136/bmjopen-2018-021704


Systematic screening for atrial fibrillation in a 65-year-old population with risk factors for stroke: data from the Akershus Cardiac Examination 1950 Study

Europace 2017 [Epub ahead of print]. DOI: 10.1093/europace/eux293
# Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE 1950 study</td>
<td>Akershus Cardiac Examination 1950 study</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AHREs</td>
<td>Atrial high-rate episodes</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes mellitus, previous Stroke (doubled), Vascular disease, Age 65-74, Sex category (female)</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>EHRA</td>
<td>European Heart Rhythm Association</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>HUNT</td>
<td>Health Survey of Nord-Trøndelag (HelseUndersøkelsen i Nord-Trøndelag)</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>NOAC</td>
<td>Non-vitamin K antagonist oral anticoagulants</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>N-Terminal fraction of the prohormone of Brain Natriuretic Peptide</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Atrial fibrillation (AF) is by far the most common sustained cardiac arrhythmia, affecting 1 in 4 during a lifetime [2]. Although irregular pulse and heart beats had been described from ancient times, the very first scientific description of ‘auricular fibrillation’ was published by cardiologist Sir Tomas Lewis in 1909 [3], who also later first described the intermittent pattern of the arrhythmia. Already then, AF was described as ‘an extremely common condition’. During the same period, in 1903, Willem Einthoven, a Dutch doctor and physiologist, invented the first electrocardiogram (ECG), and for this merit he received the Nobel Prize in Medicine in 1924. Today, 100 years later, a standard ECG is still the gold standard in diagnosing AF. Lately, the advent of smaller ECG devices (implantable, wearable or handheld) has expanded the possible application of ECG in the search for AF (Figure 1).

**Figure 1.** The development of the electrocardiogram (ECG), illustrated (to the left) by an early commercial ECG machine, alike the first electrocardiogram developed in 1903 by W. Einthoven, and (to the right) one of several handheld devices available today. Left image reprinted from Wikimedia Commons (public domain). Right image reprinted with permission from Cardia/AliveCor Inc. (San Francisco, CA, USA).

### 1.1 Definition of atrial fibrillation

AF is a cardiac arrhythmia defined by certain ECG characteristics, and an ECG is mandatory for the diagnosis. Rapid fibrillatory waves replace the P-waves seen in normal sinus rhythm. The ventricular response (QRS complexes) is usually irregular, or ‘irregularly irregular’; meaning that the irregularity of the RR intervals do not follow any repetitive pattern (Figure 2) [4].
No formal definition of the required length of the arrhythmia exists. However, it is generally accepted that a rhythm suggestive of AF should be present for at least 30 seconds, or sufficiently long for a 12-lead ECG to be recorded [4].

Figure 2. Portions of standard 12-lead electrocardiograms indicating normal sinus rhythm (upper strip), atrial fibrillation with a slow ventricular rate (middle strip) and atrial fibrillation with a rapid ventricular rate (lower strip). In sinus rhythm standard P-waves are followed by regular QRS complexes, while atrial fibrillation is characterised by absence of P-waves and irregular RR intervals. Edited from 12-lead electrocardiograms recorded in the Akershus Cardiac Examination 1950 study.

1.2 Pathophysiology

In AF, electrical impulses cause rapid and irregular contractions of the atria (>300 beats per minute). The atrioventricular node responds intermittently, due to its variable refractoriness and slowed conduction, protecting the ventricles from the extremely fast atrial rate. Atrioventricular node conduction can be influenced by the nervous system, concomitant disease or medication. During AF, ventricular rate is not controlled by the sinus node, but by the atrial rate, the refractory period of the atrioventricular node and the degree of further penetration to the infranodal conduction system of the heart [5].

Risk factors for AF, as described below, are well established. However, the precise mechanisms by which aging, hypertension and other risks increase the propensity for initiation and maintenance of AF, are less understood [6]. Still, these conditions are known to impact ‘triggers’ of AF, most commonly arising in the pulmonary veins. Triggered activity is thought to be the most common mechanism of AF in paroxysmal AF, and is one of the three mechanisms that may cause cardiac arrhythmia in general, the two others being automaticity and re-entry mechanisms [6].

The wide range of clinical presentations of AF may be due to a complex interplay between triggers and substrate for AF maintenance. The ‘AF substrate’ is caused by atrial remodelling, broadly divided into electrical and structural remodelling. Electrical changes develop within hours and days of AF, while structural remodelling is thought to take place within weeks and months of AF and is characterised by enlargement of atrial myocytes, atrial dilatation and fibrosis [7]. Predisposing diseases, such as
hypertension, coronary heart disease or heart failure, and the presence of AF itself, may cause further remodelling of the atria over time.

1.3 Epidemiology

AF is a major public health problem, due to the increased risk for hospitalisation, heart failure, ischemic stroke and death in both sexes, and particularly in women [8-11]. In addition to the suffering of millions of individuals worldwide, AF and its associated risks exerts a considerable economic burden on the healthcare system [12].

1.3.1 Prevalence

Just after the turn of the millennium, large studies of AF epidemiology reported a prevalence of ~1% in the adult population [13-15]. More recent reports suggest a prevalence of 2.0–3.5% [16-19]. All major studies have consistently reported a stepwise increase in AF prevalence by advancing age (Figure 3) [13, 17, 20-22], increasing to at least 4% at 60-69 years, and at least 13% after the age of 80 years [16, 17, 19].

The prevalence is higher in men than in women, across different age groups [17, 18, 22]. However, absolute numbers have been found to be higher in women, at least in the older age groups, as women live longer [18, 19, 23]. A higher prevalence is seen among individuals of European ancestry, compared to other ethnic groups, independent of other known risk factors [13, 24, 25]. Genetic mechanisms have been suggested to account for these differences [26].

Figure 3. Prevalence of atrial fibrillation in relation to age (based on nation-wide registry data, Sweden) [17]. A steep increase is seen after the age of 65 years. Reprinted with permission from John Wiley & Sons; Journal of Internal Medicine.
Most population-based studies of AF prevalence have relied on medical history or registry data, and standard ECG recorded at one point in time. As AF is often paroxysmal and can be asymptomatic in 30-40% [27-30], it is widely acknowledged that a large but unknown proportion of AF is unrecognised [4, 19].

In Norway, no registry data on AF prevalence have been published. The Asker and Bærum AF (ABAF) study, performed in the same geographical area as the current study, reported a prevalence of 10.0% (15.4% in men, 5.7% in women) in a 75-year-old general population, including previously undiagnosed AF in 1.1% [31]. From the Tromsø study, Nyrnes et al. reported on AF incidence among younger adults (mean age 46 years at baseline; incidence 2.7 (women) and 3.9 (men) per 1000 person-years, after 11-year follow-up) [32]. At this young age, these incidence rates were higher than reported in most other population studies [18].

1.3.2 Risk factors

A risk factor is any characteristic associated with increased risk, or chance, of developing a disease. The term risk marker is often used when causality is not established, while a determinant implies proof of causality [33]. Briefly, risk factors may also be described as either non-modifiable (inherent characteristics of an individual, e.g. sex, age or genes) or modifiable (e.g. body weight or blood pressure).

A family history of AF increases the risk for AF [34, 35], also after adjustment for other risk factors including known genetic variants of increased AF risk [36]. Hence, a family history of AF, and particularly in the case of early onset before the age of 60-65 years, may be an important factor in evaluation of AF risk.

Hypertension is the most important modifiable risk factor for the development of AF [37]. Moreover, hypertension is found in >70% of individuals with AF [38], and may contribute to further AF progression [39]. Overweight is also a major risk factor for AF, and risk increases in parallel with increased body mass index (BMI) [40, 41]. Interestingly, a few studies have reported increased risk related to body size measures other than BMI. For example, tall stature (body height) has been identified as an independent risk factor of AF, in both sexes [42, 43].

Historically, the Framingham Heart Study was the first study to extensively describe AF risk factors; identifying age, male sex, hypertension, congestive heart failure, valvular disease, diabetes and myocardial infarction as independent risk factors associated with AF [22]. Later, more risk factors have been reported, including chronic renal disease, pulmonary disease, obstructive sleep apnoea, thyroid dysfunction, excessive alcohol intake and smoking [4, 44]. Physical activity intensity has shown a U-shaped relationship to AF, as both a sedentary lifestyle and vigorous exercise seem to increase the risk for AF [45]. Inflammation and increased levels of biomarkers, such as natriuretic peptides, have also been shown to reflect increased AF risk [46].

Of note, prevention of AF has received far less attention than treatment of AF [47]. Importantly, more than 50% of AF cases can be attributed to modifiable risk factors, and elevated blood pressure and elevated BMI have been identified as the two most important contributors [37].
**Table 1. Standard classification of atrial fibrillation (AF) according to its presentation, duration and treatment strategy [4].**

<table>
<thead>
<tr>
<th><strong>Classification</strong></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First diagnosed AF</strong></td>
<td>A patient who presents with AF for the first time (irrespective of duration)</td>
</tr>
<tr>
<td><strong>Paroxysmal AF</strong></td>
<td>Recurrent AF (≥2 episodes), self-terminating usually within 48 hours, or at least within 7 days (clinically, the 48-hour period is important, as spontaneous conversion is less likely after this point).</td>
</tr>
<tr>
<td><strong>Persistent AF</strong></td>
<td>AF episode lasting longer than 7 days, or requiring termination by cardioversion, either by drugs or by direct current cardioversion.</td>
</tr>
<tr>
<td><strong>Long-standing persistent AF</strong></td>
<td>Persistent AF lasting &gt;1 year, but rhythm control is still an option under consideration.</td>
</tr>
<tr>
<td><strong>Permanent AF</strong></td>
<td>Rhythm control (restoration of sinus rhythm) is no longer possible and/or the presence of AF is accepted by the patient and the physician. Hence, rhythm control strategies are, by definition, not further pursued.</td>
</tr>
</tbody>
</table>

The typical AF patient has been thought to progress from rare (and/or short) episodes of AF to more frequent (and/or longer) episodes, before developing more sustained arrhythmia [4]. Irreversible remodelling, occurring as atrial disease progresses, is believed to contribute to sustained arrhythmia [49, 50]. However, this natural course has been debated, as exceptions frequently occur, and AF may also regress from persistent to paroxysmal [51].
### 1.5 Clinical presentation

AF most commonly presents with symptoms such as palpitations, dyspnoea or fatigue [38]. Other symptoms are chest discomfort, dizziness or light headedness, and reduced exercise capacity [4]. Accompanied anxiety is also common. Importantly, many have unspecific symptoms, and 10-40% may be completely asymptomatic [27-29, 52]. Hence, AF may remain undiagnosed until a stroke occurs [53-55], substantiating the need for early detection followed by stroke preventive treatment [56]. Early detection of AF may also positively influence other outcomes. Left ventricular dysfunction has been shown to be as prevalent in asymptomatic patients as in symptomatic patients [27], emphasising the importance of echocardiographic assessment also in asymptomatic AF patients.

The most important clinical outcomes associated with AF, are presented in **Table 2**. More recent reports have strengthened the evidence that also cognitive decline and dementia are associated with AF, even in stroke-free individuals, possibly due to cerebral microembolism [57-59].

<table>
<thead>
<tr>
<th>Event</th>
<th>Association with AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Mortality is doubled, and higher in women than in men.</td>
</tr>
<tr>
<td>Stroke</td>
<td>At least 20% of all strokes are due to AF, and a higher proportion is associated with AF. AF is also associated with higher severity of strokes.</td>
</tr>
<tr>
<td>Left ventricular dysfunction and heart failure</td>
<td>Left ventricular dysfunction is often seen in AF patients. Symptomatic heart failure and AF frequently coexist; heart failure being both a cause of AF and a consequence of AF.</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Quality of life is impaired in most but not all patients with AF.</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>Hospitalizations due to AF are frequent, have a high cost and may affect quality of life.</td>
</tr>
</tbody>
</table>

**Table 2.** Most important outcomes and consequences associated with atrial fibrillation (AF). Adapted from the European Society of Cardiology (ESC) guidelines for the management of AF [4, 60].

### 1.6 Stroke and stroke risk

AF increases the relative risk of stroke five-fold [9]. Worldwide, stroke is the leading cause of acquired disability and the second most common cause of death [61]. Approximately 30-35% of strokes seem to be associated with AF [62-65]. Importantly, strokes associated with AF are more severe and cause more disability [66], and are also associated with increased mortality [63].

It is recommended that stroke risk in AF is assessed by the CHA2DS2-VASc score [60], a widely recognised risk stratification scheme involving the most common risk factors for stroke in AF (**Table 3**) [67, 68]. A higher score indicates higher risk. Individuals with a score of 0 are truly 'low risk' with an annual stroke
rate <1%, while a score of ≥2 carries an annual stroke risk of 3% or more [69]. Among the risk factors included in the score; increased age, followed by a history of stroke, confers the highest risk [68].

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (with left ventricular dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension †</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thrombo-embolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease ‡</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3. The CHA2DS2-VASc stroke risk score. Points are added together to a maximum of 9. TIA; transient ischemic attack. †Blood pressure consistently elevated >140/90 mmHg, or antihypertensive treatment. ‡Prior myocardial infarction, peripheral artery disease, aortic plaque [60, 70].

Asymptomatic AF seems to carry the same risk of stroke as symptomatic AF [52]. Data from patients with implanted cardiac devices have shown that subclinical atrial tachyarrhythmias, also called ‘atrial high-rate episodes’ (AHREs), are associated with increased risk of both clinical AF and stroke [28]. Although some reports conclude that persistent AF carries a higher stroke risk than paroxysmal AF [71], a larger body of evidence has identified comparable stroke risk in paroxysmal and permanent AF [72-74]. Hence, it is recommended that stroke risk should be assessed regardless of AF type (paroxysmal vs. permanent, or asymptomatic vs. symptomatic) [60].

1.7 Management

Initial management, following a first-time diagnosis of AF, includes a complete history and a physical examination including a 12-lead ECG. Further investigations include basic laboratory investigations (thyroid and kidney function, electrolytes, full blood count, glucose and lipid profile), transthoracic echocardiography and, in some cases, exercise-testing. The long-term management of AF should be focused at reducing symptoms, improving quality of life, and preventing severe complications such as ischemic stroke [4].

Anticoagulant treatment with warfarin reduces the risk of stroke by approximately two-thirds [75]. More recently, non-vitamin K antagonist oral anticoagulants (NOACs; dabigatran, rivaroxaban, apixaban or edoxaban) have been shown to be as effective as warfarin, while causing fewer intracranial bleedings [60, 76]. Still, the bleeding risk is not negligible and benefit must be balanced against risk. According to the
European Society of Cardiology (ESC) guidelines for the management of AF, anticoagulation is recommended in all individuals with AF, except those (both male and female) who are truly at low risk, i.e. aged <65 years with no other risk factors according to the CHA$_2$DS$_2$-VASc score, in whom risk of bleeding is found to outweigh risk of thromboembolism [60]. Importantly, anticoagulant treatment is the only therapy shown to reduce mortality in AF [77].

The selection of either a rate or rhythm control strategy should be based on symptoms and complaints, as no prognostic value of either strategy has been shown [78, 79]. Briefly, rate control is achieved by beta-blockers or calcium channel blockers, and may in selected patients be supplemented by digoxin. A rhythm control strategy refers to any treatment directed towards restoration and maintenance of sinus rhythm, and is recommended in patients who remain symptomatic in spite of adequate rate control, or as a first option in recent onset symptomatic AF patients. Rhythm control can be divided into cardioversion, antiarrhythmic drugs or ablation procedures [4].

Optimal management of concomitant disease, often referred to as ‘upstream therapy’, may delay the development of AF in the first place (primary prevention) or, once AF is diagnosed, may decrease the rate of recurrence or progression to permanent AF (secondary prevention) [4].

### 1.8 Screening for atrial fibrillation

In the literature, terms such as ‘silent’, ‘asymptomatic’, ‘unknown’ or ‘subclinical’ AF are frequently used interchangeably. The ESC guidelines for the management of AF use the term ‘silent’ AF synonymously with ‘asymptomatic’ and ‘undiagnosed’ AF [4]. However, in the context of AF screening, the terms ‘silent’ and ‘asymptomatic’ are imprecise, suggesting complete absence of symptoms. In AF screening, any not previously diagnosed cases of AF should be of interest. Hence; terms such as ‘unknown’, ‘undiagnosed’ or ‘unrecognized’ seem more appropriate, and are used in this thesis.

Broadly, screening can be classified as either systematic or opportunistic. Systematic screening implies that a group of people or patients, e.g. above a certain age, are invited for screening. Opportunistic screening is comparable to ‘case-finding’, and is restricted to individuals who have already consulted healthcare, usually for some other purpose.

Prior to this work, the ESC guidelines for the management of AF recommended opportunistic screening for AF in all patients ≥65 years, using pulse-taking followed by an ECG in those with an irregular pulse [60].

The recommendation was based mainly on the SAFE study [80, 81]. In this three-armed study, opportunistic screening, systematic screening and usual care were compared (~14,800 participants, >65 years, mean age 75 years), concluding that opportunistic screening was as effective as systematic screening, but at a lower cost (1.6% unknown AF in both screening arms versus 1.0% detected by usual care). However, SAFE and most other studies at the time, recorded only a single, standard 12-lead ECG. Later, a systematic review of 30 single time point ECG screening studies reported an overall incidence of unknown AF of 1.0%, increasing to 1.4% in those ≥65 years [82].
Unknown paroxysmal AF is often missed by a single time point ECG. The true prevalence of AF can most likely be obtained using implantable devices providing long-term continuous rhythm monitoring [83]. In the ASSERT study, it was shown that ~35% of a cardiac patient population (≥65 years with hypertension and no history of AF) with a pacemaker or implanted defibrillator had AHREs detected during a long-term follow-up of 2.5 years [28]. Although AHREs may also represent other supraventricular tachycardias, it was shown to be associated with increased risk for clinical AF as well as stroke [28]. However, the temporal relationship between AHREs and stroke was poor, suggesting that mechanisms other than cardioembolism could be involved. In recent years, improved AF detection algorithms have been developed for implantable loop recorders, mostly tested in cryptogenic stroke populations, identifying ~25% unknown AF in this group [54].

However, implantable loop recorders are still costly, require an invasive procedure and may not be feasible or acceptable for screening in the general population. Hence, external (handheld or patch) ECG monitors have been suggested to detect unknown AF in the general population, due to their high detection rate of AF, documented accuracy, and ease of use [84-87]. Such devices have also proven more effective than traditional 24-hour ECG [53, 88, 89].

Altogether, the following aspects have contributed towards increased attention and interest in screening for unknown AF: (1) Increased knowledge of the proportion of undiagnosed AF in stroke patients; (2) increased knowledge of the proportion of undiagnosed AF in the population in general; (3) improved AF treatment options, particularly with the advent of the NOACs, and; (4) the advent and availability of new technology and new ECG modalities.

However, wide knowledge gaps still exist. Evidence of reduced stroke incidence, following systematic screening, does not exist yet. At the time of planning of the ACE 1950 AF screening sub-study, the STROKESTOP pilot study had recently reported the prevalence of unknown AF in a 75-year-old general population; a 12-lead ECG revealed 1.2% unknown AF, while a subsequent two-week screening by intermittent handheld ECG ('thumb ECG'), among those with one or more additional risk factors, revealed 7.4% unknown AF [90]. At the same time, the main STROKESTOP study, investigating a larger population of the same age, had commenced [91]. However, systematic screening of the general population at the age of 65 years had not been studied yet.
2 AIMS

1) To design a prospective, population-based cohort study suitable to investigate development and progression of AF and related cardiovascular diseases, and to perform the baseline examinations.

2) To assess sex-specific prevalence of AF, including unknown AF found by standard 12-lead ECG screening, and to investigate the prevalence of cardiovascular risk factors and their association with AF, in a cross-sectional analysis at the age of 63-65 years.

3) To investigate the diagnostic yield of systematic screening for unknown AF by two-week intermittent, handheld ECG, in a general population at increased risk for stroke at the age of 65 years (CHA$_2$DS$_2$-VASc score $\geq 2$ for men or $\geq 3$ for women).
3 METHODS AND MATERIALS

The Akershus Cardiac Examination (ACE) 1950 study is a prospective, population-based cohort study established to investigate the development and progression of AF and other cardio- and cerebrovascular diseases. Long-term longitudinal follow-up of the participants has been planned for. The current thesis is focused on the design, implementation and a cross-sectional analysis of the cohort at baseline. In addition, an AF screening sub-study was performed within the cohort (Figure 4).

3.1 Planning period and study population

3.1.1 Study population

The ACE 1950 Study was performed in Akershus County, surrounding the Norwegian capital city of Oslo. In 2011, the population was 545,653 (~11% of the population in Norway). There are two main hospitals in the county; Akershus University Hospital and Bærums Hospital (Vestre Viken Hospital Trust) (Figure 5). Basically, all adult inhabitants requiring specialised care are treated at one of these two hospitals.

The ACE 1950 study population was pre-defined as all women and men born in 1950 and resident in Akershus County at the start of the study. After ethical approval, a list of all eligible residents (n=5,827; 1,705 and 4,122 from the catchment areas of Bærums Hospital and Akershus University Hospital, respectively) was obtained from the Norwegian Population Registry (as of November 1st, 2011), including full name, date of birth, address and telephone number.
3.1.2 Study recruitment

An invitation letter was sent by standard mail, with study consent form attached. Letters were sent in bulks of 50-200 to potential participants. The invitees were asked to respond by telephone or e-mail, and received an appointment by standard mail. Non-responders were sent a remind letter approximately 6 weeks later, followed by one phone call, according to protocol. Enrolment into the study followed after written informed consent.

3.2 Baseline examinations

3.2.1 Cardiovascular examination

All participants were subjected to a structured cardiovascular examination. For measures of body size, the participants wore light clothes without shoes. Body weight was measured in kilograms (with one decimal) using an electronic medical weight scale (Seca 877). Height was measured in centimetres (without decimals) using a wall-mounted height scale (Seca 222). BMI was calculated as weight divided by the square of the height (kg/m²), and was classified as normal weight (<24.9 kg/m²), overweight (25.0-29.9
kg/m²) or obese (≥30.0 kg/m²) according to World Health Organization (WHO) standard classification [92]. Body surface area (m²) was calculated by the Mosteller formula [93]. Waist and hip circumference were measured by a manual measuring tape. Waist circumference was measured midway between the iliac crest and the lowest palpable rib, or in slim persons at the point of the minimal waist, while hip circumference was measured around the widest portion of the buttocks, as defined by the WHO [94].

After at least 5 minutes of seated rest, blood pressure was measured three times in the seated position, using the automatic monitor Carescape V100 (GE Healthcare). Overarm circumference was measured to ensure correct cuff size. The right arm was preferred, but repeat measurements of the left arm were performed in case of elevated blood pressure. The participant then rested for ten minutes in the supine position before a 12-lead electrocardiogram (ECG) with 10-second printouts (50 mm/s and 10 mm/mV) was performed (AT-101, Schiller or MAC 5500 HD, GE Healthcare). Repeated blood pressure measurements were then performed in the supine position.

Transthoracic echocardiography was performed using Vivid E9 (GE Healthcare, Horten, Norway), according to a pre-defined protocol. Images were stored electronically and analysed offline by Echopac version 201 (GE Healthcare, Horten, Norway). Regular team training, including intra- and inter-observer studies to ensure high-quality and uniform examinations, were carried out. Carotid and intracranial artery ultrasound were performed by another team of resident doctors and echo technicians.

Pulmonary function was assessed by spirometry (Vitalograph Gold Standard Model 2150; a non-electronic dry wedge type bellows spirometer), in accordance with current recommendations [95]. FEV₁ and FVC were registered as the best of three performances that varied less than 150 ml. In case of a pathological FEV₁/FVC ratio, a reversibility test was performed.

Tests of cognitive function were selected to assess all cognitive domains; (1) the 10-item wordlist test from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery [96]; (2) the Trail Making Test A and B [97], and (3) the Montreal Cognitive Assessment (MoCA) test, developed to detect early cognitive deficits by measuring global cognitive function (Norwegian version 7.1 was used) [98]. The tests were performed in this order, by a limited number of trained study personnel.

Fasting venous blood sampling was performed according to a pre-specified protocol. A total of 96.5 ml (Bærum) or 93.5 ml (Akershus University Hospital) venous blood was sampled. Within 30-60 minutes, plasma and serum samples were centrifuged at 1920 G for 20 minutes, pipetted into micro-tubes of 0.5 mL and stored in biobank facilities at each site (storage at -80°C). The local laboratory performed immediate standard analyses, using 10 ml (Bærum) or 7 ml (Akershus University Hospital) of the sampled blood. These analyses included an extended hematogram, electrolytes, creatinine, liver enzymes, thyroid hormones, lipids, fasting blood glucose and HbA1c (glycated haemoglobin). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate estimated glomerular filtration rate (eGFR) [99].

An electronic Case Report Form was constructed (Microsoft Access 2010) and used for registration of clinical data. All collected data, including 12-lead ECGs, were stored electronically at dedicated servers.
3.2.2 Questionnaires and self-reported data

All participants responded to an ‘ACE 1950 questionnaire’ (*Appendix I*), providing a detailed history of cardiovascular risk factors and diseases. Although specifically constructed for this study, the selection and phrasing of questions were harmonised with questionnaires of the *Cohort of Norway* (CONOR), a collection of standardised health data from large population-based studies in Norway [100], as well as the *Health Survey of Nord-Trøndelag (HUNT) 3 study* [101, 102]. For AF, the following question was asked: “Have you ever been diagnosed with atrial fibrillation or atrial flutter?” A positive response was followed by additional questions on AF history, symptoms and treatment (*Appendix II*).

Socioeconomic variables including marital status, residential status, education level and occupational status were registered. Questions on tobacco use, alcohol and physical activity were phrased as in HUNT 3 [101]. Questions regarding diet were collected from a previously validated questionnaire [103]. The participants also reported any known history of AF and related cardiovascular diseases among 1st degree relatives.

Current use of medication was self-reported and registered in the electronic Case Report Form according to the Anatomical Therapeutic Chemical (ATC) classification system.

Three additional and previously validated questionnaires were self-administered by all participants:

**SF-36:** The 36-item short-form (SF-36) is used to assess health-related quality of life, by a multi-item scale of eight health concepts, including limitations in physical activity, emotional and mental health and general health perception [104]. The Norwegian version has been validated [105], and normative data from Norway has been presented [106].

**HADS:** Hospital Anxiety and Depression Scale (HADS) is a 14-item form assessing symptoms of anxiety (HADS-A) and depression (HADS-D) [107]. In cardiovascular patients, it has been shown to be reliable as a screening tool for depression or anxiety [108].

**DS-14:** A 14-item previously validated questionnaire assessing the level of negative affectivity and social inhibition, to calculate a score indicative of a so-called type D personality [109]. The questionnaire is not widely used, but an association between ‘type D personality’ and elevated cardiovascular risk has been described [110].

A web-based questionnaire platform was set up (Snap Survey) for all questionnaires.

3.2.3 Validation of atrial fibrillation

All self-reported AF at baseline was validated by the author of this thesis and one cardiologist. ECG documentation present either in the hospital record or as a study ECG was required. One documented episode was considered satisfactory. The diagnosis was also considered confirmed if AF was thoroughly and repeatedly (more than once) described by a physician in the patient records, or if supportive

* Original paper version of ACE 1950 questionnaires (in Norwegian) are included as appendices, as these are previously unpublished.
documentation was found convincing, e.g. a documented history of cardioverted AF. When necessary, ECG rhythm strips were collected from primary physicians. In case only atrial flutter was found, this was counted as AF in the analyses and prevalence figures.

3.2.4 Definition of diseases and stroke risk score

Based on clinical and self-reported baseline data, we defined key variables for the current and future ACE 1950 studies:

The CHA2DS2-VASc stroke risk score was calculated for all individuals with AF, based on self-reported heart failure, myocardial infarction and stroke/transient ischemic attack (TIA). Data on vascular disease, other than myocardial infarction, was not available. Hypertension was defined as baseline mean blood pressure (from the second and third of three readings in the seated position) ≥140 mmHg (systolic) or ≥90 mmHg (diastolic), or self-reported current use of antihypertensive medication. Diabetes was defined as a self-reported diagnosis or daily use of hypoglycaemic medication, or elevated glucose tests at baseline (both HbA1c ≥6.5% and fasting blood glucose ≥7.0 mmol/l).

Further definitions of other diseases and risk factors, such as hypercholesterolemia and physical activity, are described in Paper II. Some modifications to these definitions were done in the CHA2DS2-VASc construct for the selection of a study population for the AF screening sub-study (see below, chapter 3.3.1).

3.2.5 Follow-up after study visit

Shortly after the baseline visit, all participants received a standardised summary of their main results, e.g. blood pressure, heart rhythm and a brief description of clinical biochemistry, spirometry, cognitive tests and ultrasound exams. The standard electronic medical record system 'DIPS' was used for this purpose. Abnormal findings were only conveyed in case of clinically relevant results. A list of standard phrases to be used was made to ensure uniform feedback across study personnel. If indicated, a referral for follow-up was sent either to the primary physician or to a relevant specialist.

3.3 Atrial fibrillation screening sub-study

3.3.1 Study population

The AF screening sub-study was planned during the conduct of the baseline examinations, and commenced in 2015, when the participants were 65 years (Figure 4). All participants who had at least one additional risk (other than age and female sex) according to the CHA2DS2-VASc stroke risk score (≥2 for men, ≥3 for women), but no history of AF, were identified. The risk score calculation was based on baseline data. To create a truly ‘high risk’ study population, some modifications to the original score model was done (Paper III, Supplementary Table S1). Most importantly, hypertension was defined as a blood pressure ≥160 mmHg (systolic) or ≥100 mg (diastolic), or self-reported daily use of antihypertensive medication.
In total, 1601 individuals were eligible and were sent a written invitation. One phone call was made to contact participants who did not respond to the invitation.

### 3.3.2 Handheld intermittent ECG

In this sub-study, a handheld ambulatory ECG ('thumb ECG') device (Zenicor®, Zenicor Medical Systems AB, Sweden) was used (Figure 6). The device had previously been validated and proven highly efficient for AF detection [86, 88]. At the time of planning, the device was also being used in the AF screening RCT; the STROKESTOP study [91].

The device records a bipolar extremity ECG of up to 30 seconds (Figure 7), equivalent to lead I in a standard 12-lead ECG. All recordings are transmitted to a web-based database via a built-in SIM-card.

For a diagnosis of AF to be made, at least one AF episode of 30 seconds, or at least two episodes of 10-29 seconds, had to be found. This 'detection threshold' was defined identical to the requirements of the STROKESTOP study [91].

![Figure 6. Zenicor® handheld ambulatory electrocardiogram ('thumb ECG') device used in the Akershus Cardiac Examination 1950 atrial fibrillation screening sub-study (reprinted with permission from Zenicor Medical Systems AB, Sweden).](image)

### 3.3.3 Screening visit

At the study visit, all participants were met by a study nurse or junior doctor and were provided with a handheld ECG device. Updated information on any new cardiovascular events after the baseline examination was recorded. If recently diagnosed AF became evident at the visit, the participant was still offered the examination, but was not included in the screening study.

After instructions, the first ECG recording was performed and analysed. In case of poor ECG quality or suspected arrhythmia, a second recording was done. If arrhythmia or any other pathology was suspected, a
standard 12-lead ECG was performed. Participants were then instructed to record a 30-second ECG twice daily (morning and evening) (Figure 7), or whenever they experienced palpitations or symptoms associated with AF, for 14 days. The device was then handed in at the hospital, or returned by mail.

All ECGs were assessed by a cardiac nurse or a junior doctor. Abnormal findings were reviewed by a senior doctor/cardiologist, and all findings of AF were confirmed by two senior doctors. In case of inconclusive ECGs, a repeat examination (another two-week period), a Holter (24-hour continuous ECG) or R-test (10-14-day ECG event recorder) was offered. Participants with positive findings of AF, or other pathology, were offered a consultation with one of the study doctors and further referral when needed, according to clinical AF guidelines [4, 60]. The follow-up was not formally part of the study.

Figure 7. Handheld, ambulatory, one-lead electrocardiogram (Zenicor®) recordings. Upper recording shows normal sinus rhythm. Lower recording shows atrial fibrillation. In the study, 30 second-strips were recorded (10 seconds are shown here). Reprinted from the Akershus Cardiac Examination 1950 study database (Zenicor Medical Systems AB, Sweden).

3.4 General methodology

3.4.1 Quality control and data management

The ACE 1950 study is the largest study conducted at both study sites. A number of administrative measures were taken to assure high quality data collection and control of the study. A brief description of some of these measures is included, as this has been an important part of the work for the author of this thesis.

In 2013, the Department of Medical Research (Bærum Hospital) was certified according to the International Organization for Standardization (ISO) 9001:2008 standard for quality management systems. The ACE
1950 study was selected as a ‘focus project’, and all aspects of the study, including patient information, consent and care of participants, and secure data storage, were assessed and evaluated. The process contributed towards high-quality study conduct, and we continued to perform regular risk assessments on critical aspects of the study.

One example of a risk-reducing measure performed, was the splitting of the biobank. Half of the blood aliquots of each participant were transferred for storage at a different location (Regional Research Support core biobank facility, Oslo University Hospital), while the remaining specimens were kept in the biobank at each study site. Also, extracts of collected data (i.e. manually punched data) were re-checked and validated by scientific assistants.

Throughout the study, de-identified study data were stored at dedicated research storage platforms, at each site. Later, in 2016, all collected data were transferred to the TSD (Services for Sensitive Data, hosted by the University of Oslo); a national, secure IT infrastructure for handling and storage of scientific data. A number of security measures, including two-factor user authentication, ensure a high level of privacy and security.

### 3.4.2 Participant and public involvement

Participant and public involvement has become an increasingly valued aspect of medical research during the conduct of this study. Although participants were not involved in the planning of the study, random samples of participants were asked to respond to a short questionnaire focused towards their perception of participating in the ACE 1950 study. Performed shortly after the baseline visit, the intention was to provide information that could improve the conduct of the study. The perception of the received individual feedback summary was also assessed. Furthermore, focus and efforts have been maintained towards good communication with the participants, through available phone service, a study-specific e-mail address and a website; www.ace1950.no. For the planning of future examinations of the cohort, a ‘participant advisory board’ will be established.

### 3.4.3 Statistics

No sample calculation was performed for the main ACE 1950 Study, as the study was designed to allow for various sub-studies, and the sample size was naturally defined by the complete source population; all women and men born in 1950 and resident in Akershus County.

For the AF screening sub-study, an initial power analysis was performed. The original idea was to perform AF screening in a random sample of 1,000 study participants at ‘increased risk’. We expected the AF prevalence, after the baseline ECG, to be ~5%, and assumed we could find an additional 2% by screening (total prevalence 7%). Using an alpha of 0.05, the calculated power would be 0.86 (one-sided test; one-sample inference). However, preliminary data, while the baseline examinations were still on-going, showed that the expected number at ‘increased risk’ would be ~1600 participants. In order to increase the power and improve the design, it was decided to expand the study and include all participants with additional risk factors, as defined above.
In paper II–III, prevalence figures and other categorical variables were presented as frequencies and proportions (%) and compared by the χ² test or Fisher’s exact test, as appropriate. Continuous variables were reported as mean with standard deviations (SD), and the Student’s t-test was used for between-group analysis. Continuous variables not normally distributed were reported as median with interquartile range (IQR) and analysed with the Mann-Whitney U test. P-values were two-sided and considered significant when <0.05.

A logistic regression model was used (paper II) to assess associations between risk factors and AF. All available known risk factors for AF were selected from univariate analyses based on clinical and statistical significance (p-value <0.20). Pearson correlation, as well as multicollinearity statistics, was run between each of the independent variables before inclusion in a multivariable logistic regression model. Results were presented as odds ratios (OR) with 95% confidence intervals (CI). To assess the robustness of the model, a sensitivity analysis, including all candidate variables into the same multivariable model, was performed. Furthermore, we also performed secondary analyses replacing height and weight with the more commonly used BMI, as well as body surface area.

Missing data were handled by case deletion from the relevant variable. Hence, the reported proportions represent the valid proportions. In the regression analysis, a complete case analysis was performed; only cases with complete data for all variables in the model were included in the analysis.

All analyses were performed using the Statistical Package for Social Science (SPSS) version 23.0 or 24.0 (SPSS Inc., Chicago, IL, USA).

3.4.4 Ethics

All participants provided written, informed consent before enrolment, in accordance with the revised Declaration of Helsinki. The initial study protocol was approved by the Regional Committees for Medical and Health Research Ethics in Norway, on August 18th, 2011 (ref. number 2011/1475), allowing for repeated follow-up with regard to AF and related cardiovascular events until December 31st, 2050. Minor protocol amendments have later been applied for and approved by the same committee, including amendments for the AF screening sub-study, approved on March 24th and September 10th, 2015. Assessments and approvals are available on http://helseforskning.ettikom.no (in Norwegian).

The ACE 1950 study was registered at www.clinicaltrials.gov; NCT01555411.

Extensive examinations in healthy individuals, as in our study, may reveal unintended findings and create distress among participants. This was handled by thoughtful and direct communication with the participants, while avoiding to report incident findings of no clinical relevance. Specific procedures were made for this purpose. For the AF screening sub-study, there is particularly one ethical concern. Based on available evidence, it is unknown whether AF detected by screening carries the same stroke risk as ‘normal’, clinically detected AF. All individuals who had AF detected by screening, were offered a consultation with one of the study doctors or a cardiologist, and were thoroughly informed about the risks and benefits before a decision regarding anticoagulant treatment was made.
4 SUMMARY OF RESULTS

4.1 Study design (paper I)

In paper I, we described the design and methodology of the ACE 1950 study. The paper describes how the study population was derived, and how the cohort population was enrolled and examined at the baseline examinations (upper part of Figure 8). Baseline examinations commenced on September 3rd, 2012 (April 22nd, 2013 at Akershus University Hospital), and ended on May 5th, 2015. The rationale for the selected clinical variables and questionnaires used in the study, are accounted for. These aspects have been further elaborated on in the Methods and materials chapter of this thesis.

Figure 8. Flow chart of the Akershus Cardiac Examination 1950 study and the three papers included in the current thesis
4.2  Atrial fibrillation prevalence and risk factors (paper II)

In paper II, we reported baseline characteristics of the ACE 1950 study cohort, focused on AF prevalence and associated risk factors. A total of 3,706 individuals were enrolled, from a study population of 5,827 individuals (participation rate 63.6%). Women and men were equally represented (48.8% women). Mean age was 63.9±0.7 years.

The prevalence of verified AF was 4.5% (n=165; 6.4% in men, 2.4% in women; p<0.001), including previously unknown AF in 0.3% (n=12; 0.6% in men, 0.1% in women; p<0.01).

AF individuals, among both sexes, were taller, heavier and had more cardiovascular comorbidity compared to the rest of the cohort (Table 4). A family history of AF was more frequently reported among women with AF, compared to men with AF (56.8% vs. 25.6%; p<0.001). In a multivariable analysis, sex was not found to be associated with AF, while increased height, weight, hypertension, heart failure, reduced kidney function and familial AF were all significantly associated with prevalent AF.

Among individuals with AF, the median CHA2DS2-VASc score was 1 [IQR 1-2] for men and 2 for women [IQR 2-2], and anticoagulant treatment was reported among 47%. There were no sex differences with regard to the proportions receiving anticoagulant, rate or rhythm control treatment.

<table>
<thead>
<tr>
<th></th>
<th>AF (n = 165)</th>
<th>No AF (N=3,541)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>73.3%</td>
<td>50.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>41.8%</td>
<td>21.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83.6%</td>
<td>61.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10.9%</td>
<td>4.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9.7%</td>
<td>1.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td>7.3%</td>
<td>3.6%</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10.3%</td>
<td>8.5%</td>
<td>0.41</td>
</tr>
<tr>
<td>Reduced kidney function</td>
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<td>3.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>10.9%</td>
<td>5.9%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Daily smoking</td>
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<td>14.6%</td>
<td>0.19</td>
</tr>
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<td>High level of physical activity</td>
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<td>20.9%</td>
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</tr>
<tr>
<td>Family history of AF</td>
<td>33.9%</td>
<td>19.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4. Baseline characteristics of individuals with atrial fibrillation, compared to the rest of the ACE 1950 study cohort. BMI = body mass index. TIA = transient ischemic attack. AF = atrial fibrillation. See chapter 3.2 and paper II for further definitions.
4.3 Two-week screening for atrial fibrillation by handheld intermittent ECG (paper III)

In paper III, we investigated the yield of systematic screening for unknown AF at the age of 65 years. We invited 1,601 eligible cohort participants with no history of AF and with at least one additional risk factor for stroke (CHA₂DS₂-VASc score ≥2 for men or ≥3 for women), of which 1,510 individuals participated (94.3%). Unknown AF was found in 0.9% (n=13).

Individuals with screen-detected AF had more diabetes, compared to the rest of the screened cohort (53.8% vs. 21.0%; p<0.01), while fewer had hypertension. Other than that, no differences with regard to cardiovascular comorbidity and stroke risk were found.

In three participants, AF was revealed by the ‘index ECG’ (thumb ECG at the screening visit). Four participants were diagnosed during the first week of intermittent ECGs, and six during the second week. Compliance to the screening procedure (≥20 ECGs recorded during the two-week period) was 99.5%.

The total prevalence of AF (after screening), among 65-year-olds with at least one additional risk factor for stroke (n=1742), was 7.6% (n=132; 10.0% in men, 4.3% in women).
5 METHODOLOGICAL CONSIDERATIONS

5.1 Study design and baseline data collection

5.1.1 Cohort design

The ACE 1950 study was designed as a cohort study, with planned longitudinal follow-up, by new examinations or by collection of registry data. It can also be described as a ‘closed cohort’, because all participants were enrolled at the start of the study, different from an ‘open cohort’ in which participants enter and leave the cohort at different points in time [111].

In the hierarchy of research designs, non-experimental observational studies are considered inferior to randomized, controlled trials (RCTs). However, well designed observational studies provide valuable knowledge and may also challenge the evidence of RCTs [112]. Besides, for a large number of current medical and public health issues, the RCT approach is not feasible or is simply unethical [113].

Observational research can broadly be classified into cohort studies, cross-sectional studies and case-control studies, of which prospective cohort studies usually provide the highest level of evidence [114]. Observational studies can be used to measure associations or a temporal relationship between an exposure (e.g. a risk factor, a disease, or a biomarker), and an outcome (e.g. AF). An example of one of the most recognised cardiovascular cohorts is the Framingham Heart Study, which is also a landmark study within AF epidemiology [2, 9, 10].

The ACE 1950 study builds on a long tradition of high-quality cohort studies in Scandinavia, particularly within cardiovascular medicine [115-117]. Major strengths of these studies have been the long-term longitudinal follow-up, high participation rates from the general population and access to nearly complete health registries. High impact results have emerged from these studies, such as the proof of low HDL as an important risk factor for coronary artery disease, first described in the Tromsø study [118]. Although smaller, the ACE 1950 study is designed to study novel risk markers of AF and cardiovascular diseases, particularly focused towards cardiovascular imaging and biochemical markers. Before the age of 65 years, the prevalence of cardiovascular diseases, and particularly AF, is still relatively low. However, after this age there is a significant increase in incidence and prevalence of these conditions [18, 119]. Hence, long-term follow-up starting at this age can potentially contribute towards more knowledge and new evidence of markers for subclinical disease development.
5.1.2  A cross-sectional analysis

In Paper II, a cross-sectional analysis of the cohort at baseline was performed. A defining feature, and limitation, of a cross-sectional study, is that both exposure and outcome are ascertained at the same time. Hence, only associations between observed exposures or risk factors and the outcome can be assessed. A temporal association (a risk factor preceding the outcome) can usually not be established. Exceptions can be seen in the case of inherent or long-standing ‘exposures’, such as sex or genetics which unquestionably precede any outcome [120].

5.1.3 Self-reported atrial fibrillation and other cardiovascular diseases

Information bias, or recall bias, may affect self-reported disease history, and may differ depending on the condition reported. Self-report of well-defined medical conditions seem to have a higher positive predictive value than diagnostically complex conditions [121].

Individuals who shortly before enrolment had AF diagnosed for the first time may have recalled their diagnosis more easily than individuals who were diagnosed several years ago. Further, individuals treated by rhythm control are probably more likely to recall their diagnosis than individuals who are not using any AF medication. Malmo et al. performed a validation study of self-reported AF in the HUNT study, and found a positive predictive value of 66%, lower than the 79% found in our study. The highest sensitivity and specificity of self-reported AF were found below the age of 70 years [122]. In our study, validation of negative responses to self-reported AF was not performed, and this prohibits any assessment of sensitivity, specificity or negative predictive value. Still, this may only have caused an underestimation of our reported AF prevalence.

A systematic review of AF validation studies concluded that data sources and validation procedures vary substantially across studies [123]. The same review found that many studies relied on any mentioning of AF in the hospital records, and did not necessarily demand ECG documentation. However, the review focused on validation of electronic medical data.

Previous studies have shown large discrepancies between self-reported data and registry or medical record data, but also large differences in-between various cardiovascular diseases. For example, in the Olmsted County study, agreement between self-reported and medical record data was reasonably good for hypertension, myocardial infarction, diabetes and stroke (kappa* 0.71-0.80), while the agreement for heart failure was poor (kappa 0.46) [124]. Noteworthy, self-reported stroke was found to have a relatively high rate of false-positives, but agreement was improved with higher education, age <65 years and female sex. A validation study of self-reported stroke in the Tromsø Study, found a positive predictive value of 79%, a sensitivity of ~80% and a specificity of ~99%, indicating that most (but far from all) self-reported strokes are ‘true’ strokes, while very few ‘true’ strokes are missed [125].

* Cohen’s kappa coefficient is a measure of chance-corrected agreement; in this case between self-reported and medical record data. A value of 1.00 would have indicated perfect agreement. Although controversy exists, it has been suggested that 0.41-0.60 indicates moderate agreement and 0.61-0.80 indicates substantial agreement.
Lack of validation of other cardiovascular diseases than AF, adds uncertainty to our cross-sectional analysis. We may speculate that particularly heart failure (self-reported prevalence of 1.6%) is underestimated, while stroke could possibly have been overestimated, based on the validation studies described above. In the future, validation of our prevalence data, as well as new events, can be performed by review of medical records or collection of registry data.

5.1.4 Biases and validity

Biases in epidemiological studies are often classified into three broad categories; selection bias, information bias and confounding [111]. Selection and information biases can only be reduced during the planning and conduct of a study, while confounding can be corrected for in data analysis [33].

Selection bias is particularly problematic in patient- or hospital-based cohorts, and is reduced in a population-based design such as ours. However, a low participation rate may cause bias, as non-participants often, but not always, have a worse medical prognosis than those who participate [126, 127]. Generally, participation rates in large population-based studies have declined during the last decades. Although reasons for this are largely unknown, societal trends such as a declining volunteerism and possibly also reduced trust in science, have been suggested [128]. Our participation rate of 64% was reasonably high, and compares well to the Tromsø 6 study (66%) [129]. Noteworthy, a high participation rate may more easily be obtained in our age group, as shown in the HUNT 3 study; 71% of those aged 60-69 years participated, compared to 54% overall [116].

Information bias can arise if any of the information collected is erroneous [111]; e.g. by reduced accuracy of clinical measurements or errors of data punching. Recall bias, as discussed above (chapter 5.1.3), is an important type of information bias, particularly in a study largely relying on self-reported data. The bias is reduced by standardised procedures and questionnaires, and may also be further reduced by validation against medical records or registry data.

Confounding is often described as a source of bias [33, 111], although some may also describe it as its own entity [130]. A simple definition is ‘the confusion of effects’ [111]. Confounding occurs when any exposure is associated with another variable that is also associated with the outcome of the study. The ideal way to overcome confounding is by randomisation, as done in RCTs. In observational studies, confounding cannot be eliminated, only reduced. In paper II, risk factors associated with AF were assessed by multivariable logistic regression. Adjustment by regression analysis is one method that can reduce confounding, but only from variables included in the model. Unknown variables not included in the model may represent an unknown confounding effect. Other methods used to reduce confounding in observational studies are matching (typically done in case-control studies) or stratification (creating strata, i.e. by sex) [33]. Stratification by sex was attempted in paper II, but was discarded due to the low number of women with AF (n=44).

At last, the Hawthorne effect may have an impact in the follow-up of the cohort. Study participants may have a tendency to positively change their behaviour as they participate in a study. Reasons for this are unclear, but behavioural psychological mechanisms are thought to play a role, as participants may want to
do their part to obtain ‘good’ results [33]. In our study, we can only speculate that such effects may cause increased smoking cessation or more frequent visits to the primary physician among the participants.

The validity of a study includes the impact of biases, but also other aspects:

**Internal validity** can be described as the degree to which findings of a study are correct for the particular population being studied. The internal validity depends on design, data collection, missing data, accuracy of measurements and analysis performed, and is threatened by biases through all aspects of a study [33]. For example, has the validation of AF diagnoses been performed uniformly? Internal validity is often reduced in well-planned studies and with standardized study procedures. In this regard, strengths of the ACE 1950 study were the standardized and nearly complete collection of cardiovascular clinical and self-reported data. As an example; height, weight and 12-lead ECG were available from all 3,706 participants. As reported in paper II, blood pressure and hypertension data were missing in only two participants. Self-reported data collected through questionnaires were also nearly complete.

The **external validity** of a study involves aspects of generalizability to other populations than the one studied [130]. In our case, how well does this cohort reflect the ‘true’ AF and cardiovascular epidemiology of Norway, Europe or the western world? External validity is often challenged in RCTs due to stringent inclusion and exclusion criteria. In this respect, observational population-based studies may provide a better ‘real-world’ perspective. The size of the study can also, to a certain extent, contribute towards enhanced external validity. External validity may be compromised by sociodemographic differences between Norway and other countries, or even between Akershus County and the rest of Norway. Socioeconomically, Akershus County has a higher level of education, higher income and less people on social benefits, compared to the national average. Health indicators are also better than for the country in general, with less daily tobacco users and a significantly higher life expectancy [131]. Ninety percent of the inhabitants live in densely populated areas, compared to 79% for Norway in general [132].

5.2 **Atrial fibrillation screening study**

5.2.1 **Definition of medical screening**

Screening for unknown disease is, in general, an appealing thought, as early diagnosis may reduce or avoid harmful consequences. In a broad sense, screening patients for subclinical disease is part of daily medical practice, e.g. when a preoperative chest x-ray or ECG is performed [133]. The term ‘screening’ can be perceived in different ways, and for this reason may cause confusion. Broadly, most screening can belong to one of the following categories [134]:

1. A screening test offered opportunistically to one individual
2. A screening test offered systematically to a pre-defined group or population *(as in our study)*
3. A national quality-assured ‘screening programme’ including all necessary steps to achieve the desired and evidence-based risk reduction
In general, screening is also any investigation not arising from any specific complaints from the patient [134]. Importantly, systematic screening in a defined group can be different from a ‘screening programme’. While the former typically takes place within existing clinical practice, following guideline recommendations, the latter should preferably include a separate system incorporating all steps from identifying the eligible screening population, through the organisation of the screening test itself, to delivering necessary interventions in order to reach an evidence-based outcome. The most obvious challenges in medical screening include the potential costs of screening, risks of overdiagnosis or overtreatment, and possible adverse effects. The support and treatment of those suffering from any adverse effects should also be included in a screening programme [134].

In our screening study, we assessed a systematic, non-randomised approach within a general population pre-defined only by their age and risk factors for stroke.

### 5.2.2 Biases relevant in atrial fibrillation screening

General biases in epidemiology are discussed above (chapter 5.1.4). However, there are some biases specifically applicable to all medical screening, and these are **lead-time bias, length-time bias** and **the healthy screenee effect** [134]. The possible relevance of these in the case of AF screening is discussed below.

The **lead-time effect** is defined as the time between a positive screening test and the time of onset of clinical symptoms (when the disease would have been detected by ordinary practice) [135]. Intuitively, many would argue that detecting AF earlier than in clinical practice, is solely positive, as it may increase stroke-free survival time. However, critics may argue that this is not necessarily the case. Early diagnosis by screening may increase time with diagnosis, compared to usual care, without any effect on the timing of the outcome of interest (Figure 9). The increased time may be interpreted as improved ‘survival time’ while it is really only increased ‘disease time’ [33]. The true positive effect of screening is illustrated in case C (Figure 9), in which early diagnosis by screening delays outcomes (stroke or death). So far, no studies have provided evidence of an improved survival effect from AF screening, and such effects can only be proven by a specifically designed RCT.

The **length-time effect** is well recognized within cancer screening. A slowly progressing disease (e.g. a tumour) is more likely to be detected by screening at any given point in time, compared to a fast and aggressively progressing tumour. However, the latter is well recognized (in cancer epidemiology) to carry a worse prognosis. In fact, a very slowly progressing disease may never be of any clinical importance, while it is highly likely to be detected by screening, because of its long-term presence. It is unknown whether such effects are of any relevance for AF screening. However, theoretically we may encounter an unknown subclinical AF disease entity of lower stroke risk. It has already been shown that stroke risk is higher in permanent compared to paroxysmal AF [136]. Recently, data from the ASSERT study were nuanced, as detailed analysis showed that the association to stroke was only present among those with >24 h-periods of device-detected AHREs. Shorter runs were found to pose a very low risk of thromboembolism [137].
'Lead time' is the interval between detection of any disease (e.g. atrial fibrillation) by screening and the hypothetical point in time when the disease would have been detected due to symptoms or usual care. A bias may be introduced as survival or time-to-event falsely seems to increase (case B). 'Real improved survival' (case C) can only be assessed through randomised controlled trials. Figure made by the author of this thesis, modified from Fletcher et al. Clinical Epidemiology [33], with permissions from the authors.

Some may argue that overdiagnosis is a minor problem in AF screening, as it relies heavily on solid ECG documentation. However, the link between time in AHREs or AF ('AF burden'), and stroke risk is not yet completely resolved [138]. Further, the diagnostic criterion of 30 seconds of AF is arbitrary and not evidence-based. Overdiagnosis, generally in medical screening, may be closely linked to both lead-time and length-time biases. Increasingly sensitive screening tests and a broadening of diagnostic criteria are features that should be critically assessed to avoid overdiagnosis [139].

At last, the healthy screenee effect relates to selection bias, as described above (chapter 5.1.4). Participants in population studies have been shown to have a better prognosis than non-participants, and the same phenomenon has been described in established screening programmes [134]. Our screening study was not designed to assess such effects. Still, we did assess differences in clinical characteristics between participants and non-participants to the screening study (among those who were already enrolled in the cohort), and a trend towards more morbidity among non-participants was observed.

### 5.2.3 Selection of handheld ECG device for screening

A number of devices and monitors have been developed to improve AF detection, and an important part of the current work was to become acquainted with some of these [84-87, 140, 141].

At the time of planning of the screening sub-study (paper III), Zenicor® (Zenicor Medical Systems AB, Stockholm, Sweden) was regarded the best option for handheld ambulatory ECG recordings. The device had been validated against standard 12-lead ECG with high sensitivity (96%) and specificity (92%) [86], and had been found superior to standard 24-hour ECG monitoring in detecting paroxysmal AF [88].

Logistical issues, such as a secure web-based platform for the study personnel to receive, handle and analyse all ECGs, were also of importance. These features were less developed for other handheld devices. After the commencement of our study, Zenicor Medical Systems developed an AF detection algorithm...
(integrated in their standard web-based analysis program), to reduce the burden of manual ECG interpretation. The algorithm was tested in a subgroup of the STROKSTOP Study (>3000 participants), and a negative predictive value of 99.9% and a sensitivity of 97.8% (100% on an individual level) was found [142].

Of note, most validation studies of handheld or wearable ECG devices report a high sensitivity and specificity for the detection of AF. This should not be misunderstood as a measure of the proportion of ‘true’ AF cases found. Most studies have only reported on the validity of the interpretation of the ECG, against a 12-lead ECG recorded at the same time [84-86, 141], or compared to 24-hour ECG [88, 143]. Ideally, for the selection of ECG devices for screening purposes, it would be useful to compare handheld, intermittent ECG devices against long-term continuous monitoring by implantable loop recorders, to assess ‘true’ sensitivity with regard to AF detection. Such studies have not been performed yet.

5.2.4 Selection of screening population

The study population was defined as all cohort participants with no history of AF and a CHA2DS2-VASc score ≥2 (for men) or ≥3 (for women). Hypertension at baseline (≥140 mmHg systolic blood pressure, or ≥90 mmHg diastolic blood pressure, or established antihypertensive treatment) categorised a high portion of the cohort as hypertensive (62%). For the screening study, a pragmatic approach was chosen to identify as many truly hypertensive participants as possible. Hence, a baseline measurement of ≥160 mmHg systolic or ≥100 mmHg diastolic blood pressure, or established antihypertensive treatment, was required. Of note, in the development of the Framingham AF risk prediction score, it was found that the risk of AF increased substantially when the systolic blood pressure was elevated above 160 mmHg (although continuous systolic blood pressure was used in the final risk prediction model) [144].

The age boarders of 65 and 75 years are well known from the CHA2DS2-VASc stroke risk score, and have been suggested as thresholds for AF screening [145, 146]. However, the ‘CHA2DS2-VASc’ approach does not necessarily identify the population at the highest risk of AF. Data from the Framingham Heart Study showed that CHARGE-AF score performed better than CHA2DS2-VASc at predicting AF [147]. It was also shown that AF risk tends to be overestimated in individuals with high CHA2DS2-VASc scores. CHARGE-AF includes race, age, height, weight, continuous systolic and diastolic blood pressure, use of antihypertensive medication, current smoking, diabetes and history of myocardial infarction or heart failure. Accordingly, inclusion of body size measures, and possibly also blood pressure (not merely a hypertension diagnosis) may be of interest to improve pre-test probability in AF screening. Still, most screening studies have found the highest rate of unknown AF among high-risk individuals with established cardiovascular disease [146, 148]. Simple definitions of the target population for screening are probably also useful, i.e. above a certain age, if screening recommendations should be implemented.

With regard to age, other cross-sectional screening studies have confirmed a very low yield of screening for AF before the age of 65 years [148, 149]. At the age of 65 years, the prevalence of advanced cardiovascular disease, such as heart failure or coronary heart disease, is much lower than at the age of 75 years. Hence, other risk factors for AF may be more relevant at lower age. The number of screen-detected AF in our study
was too small to conclude with regard to this, but diabetes and obesity were both found in 43% of the unknown AF cases in our study.

At last, most screening studies, including ours, have excluded known AF when defining a screening population [149-151], while others (STROKESTOP) [146] have included known AF in the screening as well as the presentation of results. The latter approach could be argued to be more holistic, aiming to improve anticoagulant treatment in all individuals with AF, not only those detected by screening. In any way, this is important to be aware of when comparing results, as the denominator (screened population) in the calculations may or may not include known AF.

5.3 Statistical methods

Cross-sectional analyses, as performed in paper II and III, are suited to assess the level of morbidity and the ‘disease burden’ in the studied population. Hence, descriptive statistical methods, including the reporting of prevalence rates (using 2 x 2 contingency tables), were used in the reporting of baseline characteristics and risk factors among individuals with AF, compared to the rest of the cohort.

We applied a logistic regression model to our baseline data (paper II), to assess the associations of known AF risk factors to prevalent AF in our study population. A sex-stratified analysis was tested, but due to the low number of AF cases (particularly in women; n=44), the analysis provided uncertain risk estimates (wide 95% confidence intervals of the ORs). Sex was then included as an independent variable, along with other risk factors known to be associated with AF. Of note, we chose to include body height and body weight as two separate variables (rather than the more commonly used BMI). This was based on existing evidence suggestive of body height being an independent marker of increased AF risk, as described previously (chapter 1.3.2). However, we suspected that body height and body weight, but also sex, were variables prone to be highly correlated. Hence, these, and all other independent variables, were assessed by the ‘collinearity diagnostics’ function of SPSS. The assumption of multicollinearity was not violated (tolerance >0.10 and VIF; variance inflation factor, <10).

We performed univariate analyses on all available and known risk factors, and included all variables with p<0.20 in the subsequent multivariable analysis. In theory, a univariate non-significant variable (p>0.20) could possibly have an effect after controlling for confounders. Hence, we performed a sensitivity analysis including all variables, but this did not provide any substantial changes to the results.

We also performed secondary analyses replacing height and weight with BMI, and with body surface area. Both these were, as expected, strongly associated with AF. However, different from the primary analysis, we found that male sex remained significantly associated with AF, while only minor changes were seen for the rest of the variables.

Logistic regression models are commonly used to analyse associations of independent variables (of any type; continuous or categorical) towards a dichotomous outcome (dependent variable; in this case AF). The main purpose of a multivariable regression model is to adjust for possible confounders. Importantly, residual confounding from unknown (or not included) variables cannot be adjusted for. In our analysis, we
included the most important known risk factors of AF. Still, in a cross-sectional analysis as ours, the results must be interpreted with caution, as they are only indicative of non-causal associations.

The results of the AF screening study (paper III) were presented using descriptive statistics only. Regression analyses to assess risk factors for screen-detected AF were considered, but were found inappropriate due to the low number of positive cases (n=13). Furthermore, a control group with no screening would be of interest. However, a larger sample size would have been needed and this was not feasible or possible within the ACE 1950 cohort.

At last, longitudinal follow-up assessing incident cases of AF would have provided better results for AF risks. The comprehensive work performed to complete the baseline examinations and the screening study, did not allow for longitudinal follow-up within the present work. However, analyses of incident AF, risk factors and markers of AF, will be performed within the ACE 1950 cohort in the near future.
6 DISCUSSION OF RESULTS

6.1 Prevalence of known atrial fibrillation

In Paper II, we reported a prevalence of validated AF (4.5%; women 2.4%, men 6.4%), including a minor proportion diagnosed for the first time at the baseline 12-lead ECG (0.3%). Approximately 2/3 of cases were paroxysmal AF (Paper II, Table 2).

The literature suggests a prevalence of AF in the general adult population in the range of 2.5-3.5% [16-18], and several reports have found increased prevalence over time [23, 152]. Most studies conclude that the aging population is the most important reason for this increase. In fact, in the Rotterdam study, aging seemed to be the only reason, as AF prevalence did not significantly increase after adjustment for increased age during the follow-up of the population [20]. However, other than age, several reports point to increased survival from other cardiovascular events, and increased AF awareness and detection, as the main reasons why increased age-specific prevalence is found [153-155].

Our finding is among the highest reported prevalence in this age group, particularly among men (Figure 10). The Rotterdam study, performed more than ten years ago, reported a much lower prevalence (1.7% at 60-64 years, 4.0% at 65-69 years) [20]. Recently, Williams et al. reported US registry data that compares well with our findings; a prevalence of 6.0% in men and 2.8% in women, but at the age of 55-64 years [156]. A systematic review, as part of the ‘Global Burden of Disease project’, reported a region-specific AF prevalence for Western Europe of 1.8% (men) and 1.0% (women) at 60-64 years, increasing to 2.8% (men) and 1.6% (women) at 65-69 years [157]. These figures are low, but a systematic review may incorporate a range of different studies with regard to study populations, diagnostic ascertainment, and documentation.

The most important prevalence studies, of which age-specific prevalence is also reported, are depicted in Figure 10. We should be cautious not to draw conclusions when relating our result to other population studies. No comparable studies have reported the prevalence of one single age cohort, such as ours. Prevalence increases year by year in this age group, as nicely illustrated by the registry data from Friberg et al. (Figure 3) [17]. Hence, age groups covering 5- or 10-year intervals are not directly comparable to our findings.

Methodological differences may explain some of the heterogeneity in reported prevalence data. First, most studies do not define sub-types of AF (i.e. paroxysmal/permanent), and many earlier studies included mostly, if not only, persistent and permanent AF. Second, data sources vary between studies. Self-reported data, ECG data, hospital data and registry data are used differently, complicating comparability. Many studies report only on hospital-based populations or registry data. Third, increased awareness and ‘surveillance’ of the population by more frequently performed ECGs, may have decreased the proportion of
Figure 10. Prevalence of atrial fibrillation in the Akershus Cardiac Examination 1950 study in relation to major prevalence studies reporting on age- and sex-specific AF prevalence. Most studies report rates for wider age intervals, e.g. 60–64 or 65-69 years, complicating comparison. Studies are selected from the most recent AF prevalence review articles [18, 154, 157-159] supplemented by a PubMed search to include any recent publications.

undiagnosed AF, followed by a corresponding higher prevalence of known AF. At last, some of the differences may be true geographical differences, due to ethnicity or environment, as indicated in some reports showing large world-wide variability [157].

In Norway, only a few reports of AF prevalence exist (Figure 11). Prevalence data from the Tromsø Study were published after our study started; the prevalence in the age group 57-66 years (validated AF prevalence after 7 years of follow-up among 50-59-year-olds) was 2.7% in women and 5.4% in men (Figure 11) [160].

Incidence (new cases per unit in time, usually per year) is important in assessment of AF epidemiology, but could not be reported from our cross-sectional analysis. As for prevalence, most studies report increasing AF incidence [156, 161]. German registry data showed an incidence of ~6 per 1000 person-years in the age-group 60-64 years [16], while the recent US data showed significantly increasing incidence and prevalence over time, in all age groups in both sexes, except in women <45 years [156]. Still, evidence is conflicting, as several studies have reported stable incidence over time, after adjustment for age [155]. In Iceland, increasing incidence over time was found only in women >65 years [23].
Figure 11. Norwegian studies of atrial fibrillation prevalence [31, 160, 162].

More standardized definitions and a more accurate understanding of the global burden of AF are strongly needed [18]. Some of the best estimates of AF prevalence are probably found in registry studies with national coverage, such as the study by Friberg et al. [17], the most recent large study assessing prevalence in a setting resembling Norway. However, the study only reported hospital-registered cases. The authors report that 22% of Swedish AF patients are cared for in primary care only, and suggest a better estimate of the total prevalence in the adult population would be 3.5% [17]. If this holds true, the total prevalence of AF after the age of 60 years, based on the same registry data, would be 9.3%. As for most studies, subclinical or unknown AF is, of course, not accounted for in these reports.

Conclusively, the three most common explanations for the increasing AF prevalence, are; (1) the general aging of the population; (2) the improved treatment and survival from other cardiovascular diseases, as many of these (e.g. myocardial infarction and heart failure) are important risk factors for the development of AF, and; (3) increased awareness and initiatives to improve AF detection, including the increased availability of new and mobile ECG technology [153, 154].

As suggested by Schnabel et al. [155], the last point of increased awareness may also represent a bias, as the increased prevalence, along with improved survival from AF, could be partially explained by a ‘lead-time effect’ (chapter 5.2.2), due to more frequently performed ECGs in patients and relevant populations. In other words, a higher proportion of the ‘pool’ of unknown AF may now be found, contributing towards a higher prevalence of known AF.

*Estimated by the author of this thesis, based on the reported age-specific prevalence data in Friberg et al., 2013.*
6.2 **Risk factors associated with atrial fibrillation**

In our cohort, individuals with AF were taller, heavier, and had more hypertension, chronic kidney disease, heart failure, and coronary artery disease than the rest of the cohort. More individuals with AF also reported a family history of AF. As in most cohorts, AF was much more prevalent in men than in women. With regard to risk factors and their association with AF, two main conclusions can be drawn from Paper II.

First, most individuals with AF at this age do not have ‘lone AF’, but rather a high level of cardiovascular comorbidities, and particularly hypertension. Modifiable risk factors for AF resemble those well known for other cardiovascular diseases, although risks such as cholesterol level and diastolic blood pressure have been shown to be inversely associated with AF [163]. Although it is well established that advanced cardiovascular diseases, such as heart failure, myocardial infarction and valvular disease, confers a higher risk for AF on the individual level [155], most current literature suggests that hypertension and obesity (or elevated BMI) are the most important modifiable risk factors for AF at the population level today, due to the high prevalence of these conditions [37, 163, 164]. Recently, data from Norway have added to this, by showing that BMI was a strong and independent risk factor of AF, among both sexes, in the Tromsø Study [165]. The burden of comorbidity in AF found in our young cohort is also in line with European observational registry data, showing a marked increase in the burden of cardiovascular comorbidity among individuals with AF the last 10-15 years [166].

Second, associations between AF and measures of body size, other than BMI, are evident in our cohort. Both men and women with AF were not only heavier but also taller, compared to those without AF. These associations prevailed when adjusted for comorbidity. The separation of body size into body weight and body height has been far less studied than BMI. However, several studies have reported increased body height as an independent risk factor of AF [42, 43, 167-170]. As indicated in our study, it has also been shown that male sex was no longer associated with AF after the inclusion of body height as a separate risk factor [42]. Recently, two large studies from Sweden and Denmark have reported strong associations between height and AF. Andersen et al. found that increased height as well as weight (independent of each other) were strongly associated with risk of AF, among >1 million Swedish men [171]. Similarly, an analysis across four decades of the Copenhagen City Heart Study, showed that height was associated with incident AF in both sexes (but more so in men), with a 35-65% higher risk per 10 cm of height [172].

Data from the Cardiovascular Health Study, specifically assessing the whole range of body size measures (including height, but also waist and hip circumference), showed that height was the strongest predictor for AF in adjusted analyses [173]. In fact, analyses showed that the inclusion of BMI, instead of height and weight separately, led to loss of information in AF risk prediction. In recent years, CHARGE-AF and other AF risk prediction models have been developed, based on large epidemiological studies [144, 170, 174]. The CHARGE-AF included both body height and weight as separate predictors of AF, and male sex was excluded as the differences in the distribution of other risk factors were thought to account for the higher AF incidence in men [174]. These risk models are, however, not yet commonly applied by clinicians.

In our study, we may assume that most participants had reached their adult height before AF was diagnosed for the first time, as maximum adult height is usually reached by the age of 20 years [175]. As
suggested by Rosenberg et al., we may speculate that taller stature in men compared to women largely explains the increased risk for AF among males [168]. Although mechanisms behind this are not fully resolved, increased atrial size is likely to be a strong mediator on the effect of height. Tall people have larger heart chamber sizes, and it is well known that atrial size is associated with increased risk of AF [22, 176]. However, in the Cardiovascular Health Study, it was reported that the effect of height on AF risk was not affected by atrial size [168]. As suggested by Andersen et al., the risk may also be affected by higher cardiac volume load over time [171], as height and body composition are strongly associated with cardiac output and stroke volume [177]. Interestingly, this could be a mechanism comparable to the one seen in endurance athletes (who often have large cardiac dimensions and elevated stroke volume)[178], in whom increased risk of AF has been observed [171, 179].

In our AF screening study (Paper III), differences in risk factor characteristics between known AF and screen-detected AF, were compared. For this particular analysis (Paper III, Table 2), we included all new AF found at baseline or by extended screening (n=21). Broadly, no major differences were found; screen-detected AF appeared to be the same ‘entity’ as clinical, known AF. The only observed difference was that of diabetes being more prevalent among screen-detected AF. The results should be interpreted with caution, due to the cross-sectional design and the relatively low number of cases. However, diabetes is well established as a risk factor for AF. A systematic review by Huxley et al. found an approximate 40% increased risk of AF among diabetics [180], and a higher risk has been reported among younger patient groups [181]. However, it is unknown whether diabetes is associated with asymptomatic AF.

The CHA2DS2-VASc score was developed to predict stroke in individuals with known AF, but has also been showed to predict incident AF in the general population [182], as well as stroke in the general population without AF [183]. As the score is already widely acknowledged, it has been suggested that the score can be used to identify high-risk individuals for AF screening [145]. Furthermore, the additive effect of biomarkers on this score, or simply on age, has also been suggested to identify eligible subjects for AF screening [184]. NT-proBNP (N-Terminal fraction of the prohormone of Brain Natriuretic Peptide) is currently used for this purpose in the STROKESTOP 2 study [185].

6.3 Screening for unknown atrial fibrillation

In our study, screening for AF identified previously unknown AF in 0.9%, and the total prevalence of AF in the screened population was 7.6%. A higher prevalence of diabetes was found among individuals with screen-detected AF, compared to the rest of the screened cohort.

The result of 0.9% is arguably an underestimate of the yield of screening at this age, as the screened population had been examined by 12-lead ECG at the baseline visit, ~1 year earlier. Already at that point, previously unknown AF was diagnosed in 12 of 3706 (0.3%) participants. Eight of these 12 were within the ‘increased risk’ group, but were not invited for further screening as AF was already diagnosed. Hence, the baseline 12-lead ECG and the subsequent two-week intermittent handheld ECG screening could be assessed together, comparable to the step-wise screening of 75-year-olds by Engdahl et al [90]. Our step-wise screening result of 1.2% screen-detected AF (21/1742) may be more relevant when comparing our results.
Figure 12. Number of atrial fibrillation screening publications by the end of 2017, illustrated by an unreviewed PubMed search; (“atrial fibrillation”[Title]) AND “screening”[Title/Abstract]).

to other studies. The proportion of screen-detected AF, among all AF in our ‘increased risk’ screening population, was 16%.

Increased attention towards screening for unknown AF has been seen in recent years, as illustrated by the increase in scientific publications over the last 5 years (Figure 12). As shown in Table 5, opportunistic screening in patients aged ≥65 years is recommended by European guidelines, and has been so since 2010, with some minor changes in the phrasing of the recommendation (in 2010, only pulse palpation was recommended, in all patients >65 years attending general practitioners) [4]. Systematic screening, however, was for the first time recommended in the ESC guidelines of 2016 [186], and evidence builds on the STROKESTOP study [146], supported by data from the ECHOES study [148] (both studies discussed below).

In contrast, American AF guidelines do not provide any specific recommendations on AF screening, other than in the context of AHREs detected from implantable devices [187]. American guidelines for the primary prevention of stroke, however, recommend active screening for AF, but primarily by pulse assessment (followed by ECG only if irregular), after the age of 65 years, and the class of recommendation is weaker (Table 5) [188]. A recent statement from the US Preventive Services Task Force concludes that evidence for screening by ECG is insufficient (Table 5) [189].

A recent position paper on AF screening from EHRA presented a review of screening studies (n=26; 3 RCTs and 23 cross-sectional studies), and found a weighted average detection rate of screen-detected AF (across all studies) of 0.9% [190]. However, a number of limitations apply to this unsystematic review, as design, age and stroke risk profile across the reported studies vary substantially. Most importantly, most studies were conducted by single time point ECG only.
## Guidelines

### Recommendation

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA/ASA; Guidelines for the primary prevention of stroke, 2014 [188]</td>
<td>Active screening for AF in the primary care setting in patients &gt;65 years of age by pulse assessment followed by ECG as indicated can be useful (class IIa, level B).</td>
</tr>
<tr>
<td>ESC; AF guidelines, 2016 [186]</td>
<td>Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients &gt;65 years of age (class I, level B). Systematic ECG screening may be considered to detect AF in patients aged &gt;75 years, or those at high stroke risk (class IIb, level B).</td>
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### Consensus document

<table>
<thead>
<tr>
<th>Statement/recommendation</th>
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<tbody>
<tr>
<td>AF-SCREEN collaboration; ‘white paper’ [145]</td>
</tr>
<tr>
<td>EHRA consensus document, 2017 [190]</td>
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<tr>
<td>USPSTF statement, 2018 [189]</td>
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### Table 5

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation</th>
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<tr>
<td>AHA/ACC/HRS; American College of Cardiology/American Heart Association Task Force and the Heart Rhythm Society. AHA/ASA; American Heart Association/American Stroke Association. ESC; European Society of Cardiology. AF-SCREEN; AF Screening International Collaboration network. EHRA; European Heart Rhythm Association. USPSTF; US Preventive Services Task Force. AF; atrial fibrillation. ECG; electrocardiogram.</td>
<td></td>
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</table>

As systematic screening >75 years was assessed by the STROKESTOP study [146], and included as a recommendation in the latest ESC guidelines for the management of AF [186], we aimed to assess the yield of systematic screening at the age of 65 years. Although handheld ECG devices have been tested in several studies, most studies have performed single time point screening only, revealing approximately 1% unknown AF across different study settings [149, 191, 192]. One single time point screening of interest in our context, was the ECHOES study; a prevalence study performed in ~4,000 participants from the general population in the UK, aged ≥45 years, suggesting a high portion of unknown AF among elderly and those with comorbidities [148]. However, studies assessing extended screening beyond single time point ECGs, in a general population setting, are scarce. The most important such studies, in comparison to our study, are depicted in Table 6.

In 2013, a study with a design comparable to ours was performed in Sweden, serving as a pilot study for the later STROKESTOP study [90]. A step-wise screening was performed; first by 12-lead ECG among 75-76-year-olds from the general population, followed by handheld ambulatory ECG for 2 weeks among those with ≥2 risk factors according to the CHADS2 risk score (i.e. heart failure, hypertension, age ≥75 years, diabetes or stroke). The first step revealed 1.2% new AF while the second step revealed 7.4% new AF [90]. In comparison, the first step of our study (paper II) disclosed 0.3% (n=3706), while the second step identified 0.9% new AF (paper III).
Table 6. Atrial fibrillation screening studies performed in a general population setting by extended/repeated electrocardiogram monitoring, comparable to the method in the Akershus Cardiac Examination 1950 study. Studies of single time point screening, or long-term monitoring by implantable devices, are not included. Sorted by year of publication.

Yrs; years. RF; risk factor (according to CHA2DS2-VASc stroke risk score, if not otherwise noted). Sec; seconds. ECG; electrocardiogram. AF; atrial fibrillation. CHADS2; a previously used stroke risk score (one point for each of the following; congestive heart failure, hypertension, age ≥75 years or diabetes, and two points for previous stroke). CHADS2 and CHA2DS2-VASc stroke risk scores are reported as the median of the complete study population, if not otherwise noted.

* Primarily general practice, but also hospital out-patients were included; hence, not strictly a general population.

** Longitudinal follow-up of RCT (including AF prevalence in control group) not yet reported.

*** Critical selection bias may be present; >100,000 invited; only 1,739 randomised.

† Denominator for screen-detected AF rate excludes those with previously known AF.

‡ Denominator for screen-detected AF rate includes those with previously known AF.

¶ CHA2DS2-VASc only reported group-wise; 3 (new AF/no AF); 4 (known AF).

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection criteria and study design</th>
<th>Method</th>
<th>Results</th>
<th>Total prevalence (after screening); stroke risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendrikx et al. 2013 [193]</td>
<td>Any age (mean 70 yrs) + 1 RF (CHADS2); cross-sectional*</td>
<td>Handheld ECG (Zenicor), 10-sec, twice daily, 28 days</td>
<td>3.8% new AF (35/928) †</td>
<td>Known AF excluded; CHADS2 2</td>
</tr>
<tr>
<td>Engdahl et al. 2013 (STROKESTOP pilot) [90]</td>
<td>75 yrs + 1 RF; cross-sectional</td>
<td>Handheld ECG (Zenicor), 30-sec, twice daily, 2 weeks</td>
<td>7.4% new AF (30/403) †</td>
<td>14.3%; CHADS2 1.85 (mean)</td>
</tr>
<tr>
<td>Svennberg et al. 2015 (STROKESTOP) [146]</td>
<td>75 yrs; RCT**/cross-sectional</td>
<td>Handheld ECG (Zenicor), 30-sec, twice daily, 2 weeks</td>
<td>3.0% new AF; (218/7173) ‡</td>
<td>12.3%; CHA2DS2-VASc 3(-4) ¶</td>
</tr>
<tr>
<td>Berge et al. 2017 (ACE 1950) [150]</td>
<td>65 yrs + 1 RF; cross-sectional/cohort</td>
<td>Handheld ECG (Zenicor), 30-sec, twice daily, 2 weeks</td>
<td>0.9% new AF; (13/1510) †</td>
<td>Known AF excluded (total prevalence in cohort with risk factors; 7.6%); CHA2DS2-VASc 3</td>
</tr>
<tr>
<td>Hakcox et al. 2017 (REHEARSE-AF) [151]</td>
<td>≥65 yrs + 1 RF; RCT/cross-sectional</td>
<td>Handheld ECG (AliveCor), 30-sec, twice weekly, 12 months</td>
<td>3.8% new AF (screening; 19/500) vs. 1.0% new AF (control; 5/501) †</td>
<td>Known AF excluded; CHA2DS2-VASc 3</td>
</tr>
<tr>
<td>Steinhubl et al. 2018 (mSToPS) [194]</td>
<td>≥65 yrs (women) or ≥55 yrs (men); RCT***/cross-sectional</td>
<td>Continuous ECG (Zio patch), 2 x 2 weeks</td>
<td>5.1% new AF (screening; 46/908) vs. 0.6% new AF (control; 5/831) †</td>
<td>Known AF excluded; CHA2DS2-VASc 3</td>
</tr>
<tr>
<td>Ghazal et al. 2018 (primary care) [195]</td>
<td>70-74 yrs; cross-sectional</td>
<td>Handheld ECG (Zenicor), twice daily, 2 weeks</td>
<td>5.5% new AF (16/290) †</td>
<td>12.0%; CHA2DS2-VASc 3(-4) ¶</td>
</tr>
</tbody>
</table>
Most reported screening studies, including ours, have not compared detection of AF by screening to routine practice; i.e. by a randomized controlled design. A Cochrane review performed in 2016 identified only one study fulfilling such criteria [196], namely the SAFE study (described above; chapter 1.8.2), in which single time point ECG screening were investigated and compared to usual care [80, 81].

In 2015, just after our screening study commenced, the primary STROKESTOP results were published. The study was the first large RCT on AF screening after the SAFE study, and the very first RCT to investigate systematic screening by intermittent ECG recordings (7173 participants, aged 75-76 years; Table 6). Unknown AF was identified in 3.0%, and a total of 5.1% had AF but did not receive anticoagulant treatment; a highly clinical relevant point. As part of the study, anticoagulant treatment was initiated in 93% of participants with previously unknown AF, and in 47% of those with known but untreated AF. The total prevalence of AF after screening was 12.3% [146].

As a consequence of the natural course of AF, frequently progressing from paroxysmal to permanent, observational data has shown that a higher proportion of permanent AF is found among the elderly, and those with much comorbidity [39]. Hence, it could be hypothesized that although the total prevalence of AF is lower at 65 years, compared to 75 years, the proportion of paroxysmal and undiagnosed AF could be higher. However, we found the opposite in our study, as 16% of all cases were identified through screening (compared to 24% in the STROKESTOP study).

Recently, two other RCTs have presented their results of AF screening. Unlike the STROKESTOP study, these were not designed to assess the effect on stroke incidence, but rather aimed to assess the yield of screening in an intervention group compared to a control group with no intervention (usual care).

First, the REHEARSE-AF, performed in the UK, studied a population comparable to ours; 65 years (or older) and CHA2DS2-VASc ≥2 [151]. A total of 1,001 participants were randomised to usual care or screening by handheld, ambulatory ECG (AliveCor, as shown in Figure 1) twice a week, for 12 months. Screening identified nearly 4 times as much AF compared to usual care (Table 6). Compliance was good, with 74% not missing a single week during the one-year period. However, it can be argued that screening throughout one year is less feasible in a real-life setting. Interestingly, compliance was not compromised by age; those >80 years had the same compliance as younger participants. This finding may be of interest when planning screening studies using handheld and mobile technology.

Second, the mSToPS trial was performed in a US general population derived from a health insurance registry. All participants (n=2820; mean age 74 years; median CHA2DS2-VASc 3.0) were offered continuous screening by iRhythm ZioXT (a skin-adhesive patch for continuous ECG monitoring), but participants were randomized to immediate or delayed screening. Screen-detected AF was found among 5.1% in the immediate monitoring group, compared to 0.6% found by standard care (before screening was performed within the delayed group) (Table 6) [194]. In this way, the yield of screening could be compared to standard care, while still offering screening to all participants, immediately or delayed. However, the high prevalence of screen-detected AF found in the mSToPS trial must be seen in the light of a highly selected study population. Computer models were used to select a study population based on projected risk of AF among >100,000 members of an insurance programme (introducing a profound selection bias), ending up randomising only 1,739 of these. Hence, this study was not performed in a truly general population setting.
Still, the study design is interesting and pioneering as it was a ‘site-less’ study, performed only by the use of registries, internet and mailing of ECG devices [194].

Most screening studies, including ours, have only reported the ‘point prevalence’ of unknown AF. The question of how frequently screening should be carried out, or whether it could be a ‘one-off’ screening, has not been answered. Repeated screening can theoretically detect more AF at an earlier point in time, but at a higher cost. A Swedish simulation study, modelling more than 2 billion different designs of screening programs for unknown AF, found that the ‘optimal screening program’ in a cost-benefit perspective, would be repeated screening for AF, by handheld ambulatory ECG, at the age of 65, 75 and 80 years [197]. The additive yield of repeated screening could potentially be tested in the ACE 1950 cohort, at a higher age, in the future.

Taken together, it may be argued that the yield of systematic screening at the age of 65 years is too low, even with the addition of stroke risk factors. As shown in Table 6 the yield of screening is higher at higher age, in populations with more risk factors, or with more intensive screening. Still, it may be argued that the yield at 65 years might be higher in a setting different from ours, as our two-week intermittent screening result compares well with findings from just single time point screening elsewhere [82, 190]. We may hypothesise that increased awareness of AF, both in the population and among health personnel, combined with the setting of our study; an area with good access to a government-financed healthcare system, has already led to increased detection of previously unknown AF, through standard care. This may as well explain why the prevalence of previously known AF in our cohort was relatively high. Based on our results and current evidence from other studies, we cannot draw any conclusions with regard to systematic screening at the age of 65 years, except that the yield is relatively low even in a selected group at increased risk.
The Wilson and Jungner WHO criteria for screening, or ‘Principles of early disease detection’ [1], have frequently been assessed in AF screening reports, and the apparent fulfilment of all or most of these criteria have been used as an argument that organised screening must be implemented [198-201]. However, this was not the original intention of the authors, as they merely suggested that the fulfilment of the criteria warranted further inquiry and research trials to assess the effect of screening of that condition [1]. Additional criteria on efficacy, informed participation and legal matters have been added by many national health authorities, including the Norwegian Directorate of Health [202]. In the following, AF screening is discussed with respect to the ten original WHO criteria:

1. **The condition sought should be an important health problem.**

   Wilson and Jungner originally declared that the condition ‘not necessarily need to have a high degree of prevalence, though that would be a usual requirement’. Alternatively, it could be sufficient that the condition has ‘serious consequences to the individual and his or her family’. AF meets both conditions. AF prevalence is high after the age of 65 years [17, 18, 31, 146]. Furthermore, AF is a risk factor for stroke and is associated with increased mortality [9, 10, 155].

2. **There should be an accepted treatment for patients with recognized disease.**

   Anticoagulant treatment reduces the risk of stroke by >60% [75], and is recommended by international guidelines [186, 187]. However, whether screen-detected AF confers the same stroke risk, and should be treated in the same manner as clinically detected AF, has not been confirmed in randomized trials. Still, numerous studies have reported equal or worse stroke risk and stroke incidence in asymptomatic AF (resembling the situation in which AF is detected by screening), compared to symptomatic AF [52, 203, 204].

3. **Facilities for diagnosis and treatment should be available.**

   This criteria largely depends on whether we should consider a national, systematic screening programme, demanding ‘screening centres’, or if screening should be carried out within existing (primary or specialist) health services. The latter will add a significant burden on existing services and may not be realistic. However, new technology and handheld ECG may ease the burden, by innovative web-based solutions, as tested in the mSToPS trial [194]. The AF-SCREEN network recently concluded that screening facilities for AF most likely will have to be country- and healthcare-specific [145].

4. **There should be a recognizable latent or early symptomatic stage.**

   It is well recognized that AF is asymptomatic in many, although the proportion varies roughly between 25-40% across different settings [146, 203, 205].
5. **There should be a suitable test or examination.**

The 12-lead ECG is widely available and recognized as the gold standard for the diagnosis of AF [186]. However, a variety of alternative ECG modalities exists; such as handheld ECG, patch ECG and implantable devices. Non-ECG screening tests also exists, such as modified blood pressure monitors [206] and wearable devices based on photoplethysmography technology [207]. Screening simply by pulse palpation is still recommended by many guidelines (Table 5). However, pulse palpation has a low specificity for AF [140]. Most importantly, and different from other medical screening settings, an ECG provides an immediate result and serves both as a screening test and a diagnostic test. This has important practical implications, as most of those screened immediately can be reassured that their test was negative [198]. Still, among all available devices, it is unclear which one would be the most suitable for AF screening.

6. **The test should be acceptable to the population.**

ECG is a well-established non-invasive test without any concurrent risk. New technology is likely to ease the acceptability as screening can be performed anywhere. However, general acceptance and knowledge of AF screening in the population, has not been studied well. In the SAFE study, only 3.7% found the screening visit ‘inconvenient’, as reported in a post-screening questionnaire [81]. The relatively low participation rates in the two largest RCTs (~50%), need further elucidation if screening programmes are to be implemented [80, 146].

7. **The natural history of the condition, including development from latent to declared disease, should be adequately understood.**

Although underlying mechanisms of AF are not fully understood, the clinical presentation from latent (subclinical or asymptomatic) to declared (paroxysmal/permanent and symptomatic) disease is well known, and the complications, such as stroke, are extensively proven [186, 208].

8. **There should be an agreed policy on whom to treat as patients.**

Definition of AF and in whom treatment should be initiated, is well established in current guidelines [186]. However, controversies still exist towards the duration and burden of AF required to initiate anticoagulant treatment. This is a particular concern with regard to AHREs recorded on implantable devices [209].

9. **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.**

In the SAFE study, it was found that opportunistic single time point screening above 65 years of age was likely to be cost-effective [81]. The same conclusion was arrived at for 2-week intermittent screening at the age of 75 years, based on STROKESTOP data [210]. Uncertainties still exist, as these models seem to assume that the benefit is the same in screen-detected AF as in clinically detected AF. Other uncertainties also exist, such as compliance to anticoagulant treatment in screen-detected AF [211]. However, cost-effectiveness of NOAC treatment in ‘normal’ AF patients has been well demonstrated [212].
10. **Case-finding should be a continuing process and not a “once and for all” project.**

Repeated screening has not been investigated in a large study setting, and this warrants further exploration. Current recommendation to perform opportunistic screening in all patients >65 years seeking medical care can, in principal, easily be implemented. However, it will demand resources and adaptations within our current healthcare system.

In summary, many of the WHO criteria are met but not all, paving the way for large-scale trials providing more final evidence, as suggested by Wilson and Jungner [1]. Questions remaining are: What is the most suitable target population for screening? What ECG device is best suited for screening? How should screening be organised? And, can the potential benefit of wide-scale screening outweigh the costs, including higher number of bleeding events caused by increased use of anticoagulants? Other aspects, such as the potential anxiety created among screened individuals, must also be explored. Most importantly, conclusive evidence on the effect of screening on hard endpoints, primarily stroke incidence, is needed.
8 CONCLUSIONS

1) A cardiovascular age cohort, the ACE 1950 study, was designed and 3,706 women and men from the general population, all born in 1950, have been enrolled and completed a comprehensive baseline examination.

2) Single time point screening by standard 12-lead ECG identified a low proportion of 0.3% subclinical AF at the age of 63-65 years. The prevalence of AF (4.5%) was higher than previously reported before the age of 65 years.

3) A large majority of individuals with AF had one or more cardiovascular comorbidities. Body height, weight and cardiovascular comorbidities, but not sex, were associated with AF.

4) Two-week intermittent screening by handheld ambulatory ECG identified previously unknown AF in 0.9% of 65-year-olds with at least one additional risk factor for stroke (CHA₂DS₂-VASc score ≥2 for men or ≥3 for women).
9 IMPLICATIONS

The clinical implications of the ACE 1950 study at this point, are scarce. However, longitudinal follow-up of the cohort may provide clinically relevant results, particularly with regard to AF and cardiovascular risk prediction.

Still, AF remains a common condition in clinical practice, and knowledge of its epidemiology in Norway has been scarce. The current work adds knowledge of the burden of AF and other cardiovascular diseases just before the age of 65 years. We found a high occurrence of concomitant cardiovascular diseases and risk factors in individuals with AF, and particularly a high burden of hypertension and obesity.

We have confirmed that the prevalence of diagnosed AF is comparable to other countries, if not higher. Although speculative, the high prevalence of known AF and the low prevalence of unknown AF found by screening, may suggest that AF detection through usual care is reasonably good in Norway. Still, our screening study indicates that at least 16% of AF in this group is unrecognised and untreated, underlining a potential for improved detection.

AF screening will remain an important research field in the coming years. The yield of ~1% screen-detected AF in 65-year-olds with additional risk factors for stroke, may have implications for the selection of future study populations. We may suggest that a higher ‘age threshold’ should be sought for if systematic screening is to be implemented. Still, opportunistic screening for AF by single time point ECG is already recommended in patients after the age of 65 years [186]. Handheld ECG devices, as shown in our study, can make it easier to comply with this recommendation. Such devices have, after this study, been introduced in the daily practice at our hospital.

The ultimate implication of all AF screening research, of which this study adds only a small piece to the puzzle, would be to reduce the burden of the growing AF epidemic and, particularly, to reduce the burden of AF-related strokes.
In the ACE 1950 study, it is now >3 years since the baseline examinations were performed. Collection of cardiovascular events from national registries is currently being planned, and will provide data for future projects and sub-studies within the cohort, e.g. the role of biochemical and echocardiographic markers in prediction of incident AF. In Norway, all citizens have an 11-digit personal identification number enabling linkage to nation-wide registries, such as the Cause of Death Registry and the National Patient Registry.

Epidemiological AF studies have been based on heterogeneous sources of data. Large and well-characterised cohorts, supplemented by registry data, may provide the best evidence towards increased understanding of AF epidemiology. In Norway, there is an untapped potential to investigate nation-wide AF prevalence and incidence by utilising existing nation-wide patient registry data.

For AF screening, a number of questions remain unanswered, as described above (chapter 7). Ongoing studies may provide valuable evidence towards these questions [146, 185, 213]. Recently, 5-year follow-up data from the non-randomised STROKESTOP pilot study suggested a reduced incidence of stroke after screening, based on stroke registry data [214]. The STROKESTOP study is expected to provide evidence on the effect of screening on stroke incidence [146]. Furthermore, a large RCT expected to recruit 120,000 patients >65 years for AF screening by handheld ECG, is being planned within UK primary healthcare [215]. A recent consensus statement from EHRA agreed on an 18-item list of AF research fields that should be prioritized. The statement called for more research to determine effective strategies for AF detection in patients at risk for AF and stroke [216].

New technology, both ECG monitors and ‘wearable’ technology, and their potential for AF detection, should be further explored in research trials. While smartwatches were previously equipped only with heart rate detection algorithms, studies are now applying AF detection algorithms to commercially available smartwatches or smartphones. These algorithms, based on complex analyses of heart or pulse wave variability, periodicity and complexity, have shown reasonable performance in clinical validation studies [207, 217, 218]. So far, the clinical application of this technology may be debated. However, it serves as an illustration that it is hard to foresee how AF will be diagnosed in 5-10 years from now. High-quality studies to assess such new methods for AF detection may provide guidance.

‘Pre-screening’ for AF with the biomarker NT-proBNP followed by ECG screening if elevated, is currently being tested in the STROKESTOP 2 study [185]. Future research on AF biomarkers, imaging and ‘AF burden’ may provide evidence that our current classification into paroxysmal or permanent AF is inadequate or inexpedient. Increased understanding of atrial disease mechanisms (e.g. ‘atrial cardiopathy’) is needed, and may give rise to more refined classification systems, possibly followed by improved risk stratification.

The ACE 1950 study, with its large biobank and extensive echocardiography data from all participants, can be well suited to address these issues, and may in the future fill some of these knowledge gaps.
References


166. Proietti M, Laroche C, Nieuwlaat R, Crijns H, Maggioni AP, Lane DA, … Euro Heart Survey on AFI. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium. J Am Heart Assoc, 2018. 7(9).


Appendix I

**Til deltaker:**

*Vi ber om at du fyller ut dette og de andre vedlagte skjema før du kommer til oss.*


Velkommen til undersøkelse!

Med vennlig hilsen

ACE 1950-studien
Avdeling for medisinsk forskning, Bærum sykehus
Del A: Bakgrunn

   - [ ] Ingen
   - [ ] Ektefelle/samboer
   - [ ] Andre personer over 18 år
   - [ ] Andre personer under 18 år


---

ACE 1950 – baseline spørreskjema – versjon 7.0 – 16.04.2013
Del B: Sykehistorie

5. Har du foreldre, søsken eller barn som har, eller har hatt, følgende sykdommer? 
   *Sett ett eller flere kryss pr. linje.*

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- **Atrieflimmer**
  - ("hjerteflimmer")
- **Hjerneslag eller hjerneblødning før 60-års alder**
- **Hjerteinfarkt før 60-års alder**
- **Kronisk bronkitt/KOLS/emfysem**
- **Diabetes ("sukkersyke")**
- **Nyresykdom (ikke nyresten, urinveisinfeksjon, urinlekkasje)**
- **Demens (Alzheimer eller annen type)**

Kommentarer: ______________________________________________________________
__________________________________________________________________________

6. Har du noen gang, hos lege, fått påvist for høyt blodtrykk?

   □ Ja   □ Nei   □ Vet ikke

Hvis ja, hvor gammel var du første gang du fikk påvist dette? (ca. alder) _______
7. Har du brukt, eller bruker du blodtrykksmedisin?

☐ Ja, bruker nå  ☐ Har brukt før, men ikke nå  ☐ Aldri brukt

Hvis du bruker slik medisin nå, eller har brukt dette før:
Omtrent hvor gammel var du første gang du begynte med slik medisin?

(ca. alder) ______

8. Har du, eller har du noen gang hatt, angina pectoris ("hjertekrampe")?

☐ Ja  ☐ Nei

Hvis ja, hvor mange ganger pr. uke har du merket slike smerter i løpet av den siste måneden?

☐ Ved anstrengelse, antall ganger _____

☐ Når du er i ro om dagen, antall ganger ______

☐ Om natten, antall ganger _____

9. Har du hatt hjerteinfarkt?

☐ Ja  ☐ Nei

Hvis ja, hvor mange ganger har du hatt dette? _________

Hvis ja, hvor gammel var du første gang du fikk hjerteinfarkt? (ca. alder) _________


☐ Nei  ☐ Hjerteoperert med "bypass"

☐ Hjerteoperert med klaffeoperasjon (innsetting av ny hjerteklaff)

☐ "Blokket" ut årer på hjertet med innsetting av stent

☐ "Blokket" ut årer på hjertet uten innsetting av stent  ☐ Vet ikke
11. Har lege sagt at du har hjertesvikt (svakt hjerte, vann på lungene, hovne ben)?

- [ ] Ja
- [ ] Nei

Hvis ja, hvor gammel var du første gang du fikk hjertesvikt? *(ca. alder)* _________

---

12. Har du noen gang opplevd hjertebank og/eller hyppige ekstraslag (følelse av uregelmessig hjerterytme, ”hoppende” hjerte)?

- [ ] Ja
- [ ] Nei

Kommentarer: ________________________________________________________

---

13. Har du noen gang fått diagnosen atrieflimmer eller atrieflutter (også kalt ”hjerteflimmer” eller ”forkammerflimmer”)?

- [ ] Atrieflimmer
- [ ] Atrieflutter
- [ ] Nei

Kommentarer: ________________________________________________________

---

14. Har du noen gang fått påvist andre hjerterytmeforstyrrelser?

- [ ] Ja
- [ ] Nei

Type/kommentarer: _____________________________________________________

---

*Neste spørsmål i dette skjemaet er nr. 23.*

*Spørsmål nr. 15 – 22 skal kun besvares hvis du har kjent atrieflimmer eller annen arytm. Disse spørsmålene vil du i så fall få utdelt når du kommer til undersøkelse.*

---
I de følgende to spørsmålene ber vi deg om å beskrive eventuelle begrensninger og tungpust ved fysisk aktivitet.

23. Kryss av i den boksen som passer best for deg (bare ett kryss).

☐ Ingen begrensninger ved fysisk aktivitet. Vanlig fysisk aktivitet gir ingen uvanlig tretthet, tungpust eller brystsmarter.

☐ Lett begrensning av fysisk aktivitet, men ubesværet i hvile. Vanlig fysisk aktivitet gir tretthet, tungpust eller brystsmarter.

☐ Betydelige begrensninger i fysisk aktivitet, men ubesværet i hvile. Selv små fysiske anstrengelser gir tretthet, tungpust eller brystsmarter.

☐ Umulig å utføre noen som helst fysisk anstrengelse. Periodevis også tungpust eller brystsmarter i hvile.

24. Kryss av i den boksen som passer best for deg (bare ett kryss).

☐ Aldri tungpusten bortsett fra under hard trening.

☐ Jeg blir tungpusten når jeg har det travelt eller går opp slake motbakker.

☐ Jeg må gå langsommere enn mine jevnaldrende fordi jeg blir tungpusten, eller jeg må stoppe for å puste ut når jeg går i mitt eget tempo.

☐ Jeg må stoppe etter å ha gått ca 100 meter, eller etter få minutter i flatt terreng.

☐ Jeg er for tungpusten til å forlate huset, eller jeg blir tungpusten når jeg kler av og på meg.

25. Har du hjerteklaffsykdom (klaffelekkasje eller trang hjerteklaff)?

☐ Ja  ☐ Nei

Kommentar: ________________________________________________
26. Har du en medfødt hjertesykdom (fra fødsel, oppdaget i ung eller voksen alder)?

☐ Ja ☐ Nei

Hvis ja, når ble denne oppdaget?

☐ Ved fødsel
☐ Oppdaget i ung alder
☐ Oppdaget i voksen alder

27. Har du eller har du noen gang hatt sykdommen diabetes (”sukkersyke”)?

☐ Ja ☐ Nei

Hvis ja, hva slags diabetes har du / har du hatt? (sett eventuelt flere kryss)

☐ Diabetes type 1 ☐ Diabetes type 2
☐ Svangerskapsdiabetes (forbigående i forbindelse med graviditet)

Hvis ja, hvor gammel var du første gang du fikk diagnosen diabetes? (ca. alder)_______

28. Har lege sagt at du har nyresvikt (svekkede nyrer, dårlig nyrefunksjon)?

☐ Ja ☐ Nei
29. Har du noen gang hatt hjerneslag (blodpropp eller blødning i hjernen) eller ”hjernedrypp” (TIA, det vil si at symptomene forsvant helt innen 24 timer)?

☐ Ja ☐ Nei

Hvis ja, hvor gammel var du første gang du fikk hjerneslag eller ”hjernedrypp”/TIA?

(ca. alder) __________

Hvis ja, hvor mange ganger har du hatt hjerneslag eller ”hjernedrypp”/TIA?

☐ 1 gang ☐ 2 ganger ☐ 3-4 ganger ☐ 5 ganger eller mer

Hvis ja, hvordan påvirker det i dag ditt funksjonsnivå og din evne til daglige gjøremål? Med vanlige daglige gjøremål menes f.eks. spising, påkledning, toalettbesøk (Sett ett kryss ved det funksjonsnivået som passer best).

☐ Ingen symptomer og ingen funksjonssvikt. Samme tilstand som før hjerneslaget.

☐ Ingen nevneverdig funksjonssvikt. Har noen symptomer, men klarer å utføre alle oppgaver og aktiviteter som før hjerneslaget.


☐ Moderat funksjonssvikt. Trenger litt hjelp i daglige gjøremålene, men klarer å gå uten hjelp fra en annen person.


☐ Svært alvorlig funksjonssvikt. Trenger konstant tilsyn og hjelp fra andre.

30. Har du nå eller tidligere fått påvist for lavt eller for høyt stoffskifte?

☐ Nei, aldri ☐ Lavt stoffskifte (hypotyreose) ☐ Høyt stoffskifte (hypertyreose)

Hvis ja, hvor gammel var du første gang? (ca. alder) __________
31. Har du vanligvis noen av de symptomene som er listet opp nedenfor selv om du ikke er forkjølet?

- Hoste
  - Ja
  - Nei
- Oppspyt fra brystet
  - Ja
  - Nei
- Piping i brystet
  - Ja
  - Nei

32. Har du fått behandling med antibiotika (f.eks. "penicillin") mot lungebetennelse eller bronkitt i løpet av de siste tre årene?

- Ja
- Nei

Hvis ja, hvor lenge var det siden?

- 0-3 mnd
- 4-12 mnd
- 13-24 mnd (1-2 år)
- 25-36 mnd (2-3 år)

33. Har du noen gang fått diagnosen astma, kronisk bronkitt eller KOLS/emfysem?

- Ja
- Nei

Hvis ja, hvilken diagnose?

- Astma
- Kronisk bronkitt
- KOLS/emfysem

Hvis ja, hvor gammel var du første gang du fikk diagnosen? (ca. alder)________
34. Hvor mange timer sover du gjennomsnittlig i døgnet? _________

35. Har du noen gang fått diagnosten søvnapne?

☐ Ja ☐ Nei

36. Har du noen gang hatt blodpropp i armer/ben, lunger eller andre steder i kroppen (dyp venetrombose eller lungeemboli)?

☐ Ja ☐ Nei

Hvis ja, i hvilke del/deler av kroppen har du hatt blodpropp? (Sett ett eller flere kryss)

☐ Armer/ben
☐ Lunger
☐ Andre steder i kroppen

Hvis ja, når hadde du dette første gang? (ca. alder) _____________

37. Har du vært innlagt på sykehus i løpet av de siste 12 måneder?

☐ Ja ☐ Nei

_Noter gjerne både navn på medisin, dose og antall ganger du tar medisinen hver dag._

|__________________________________________________________________________|  |
|__________________________________________________________________________|  |
|__________________________________________________________________________|  |
|__________________________________________________________________________|  |
|__________________________________________________________________________|  |
|__________________________________________________________________________|  |
|__________________________________________________________________________|  |

39. Hva var din fødselsvekt?

- □ Mindre enn 2,5 kg
- □ 2,5 – 3,2 kg
- □ 3,2 – 3,9 kg
- □ 3,9 – 4,5 kg
- □ Over 4,5 kg
- □ Vet ikke
Del C: Livsstil og kosthold

Med mosjon mener vi at du f.eks. går tur, går på ski, svømmer eller driver med trim/trening/idrett.


☐ Aldri
☐ Sjeldnere enn en gang i uka
☐ En gang i uka
☐ 2-3 ganger i uka
☐ Omtrent hver dag

Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? Sett ett kryss der det passer best.

☐ Tar det rolig uten å bli andpusten
☐ Tar det så hardt at jeg blir andpusten og svett
☐ Tar meg nesten helt ut

Hvor lenge holder du på hver gang? (Ta et gjennomsnitt)

☐ Mindre enn 15 minutter
☐ 15-29 minutter
☐ 30 minutter til – 1 time
☐ Mer enn 1 time

Med fysisk aktivitet mener vi all hverdagslig aktivitet utover å sitte/ligge i ro, som f.eks. det å være fysisk aktiv på arbeid, gulvwask, å gå til butikken samt all trening/mosjon.

41. Har du vanligvis minst 30 minutter fysisk aktivitet daglig på arbeid og/eller i fritida?

☐ Ja  ☐ Nei
42. Hvis du er i arbeid, hvilket kommunikasjonsmiddel bruker du til og fra jobb?
(Hvis transportmiddel varierer, kryss av for det du bruker mest i løpet av et år)

- [ ] Bil
- [ ] Buss/trikk/tog
- [ ] Sykkel
- [ ] Går til jobb
- [ ] Annet: ___________________________________
- [ ] Er ikke i arbeid

43. Hva er avstanden til og fra ditt bosted og arbeidsplass?

Ca. antall kilometer (en vei): __________________________

---

**KOSTHOLD**

44. Hvor mange skiver brød spiser du vanligvis? *(Sett ett kryss for hver type brød – eller porsjoner musli/kornblanding)*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Loff/fint brød</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Kneipp/mellomgrovt</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Grovt brød</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Grovt knekkebrød</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Fint knekkebrød</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Musli/kornblanding</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

45. Hvor ofte spiser du vanligvis disse måltidene? *(Sett ett kryss pr. måltid)*

<table>
<thead>
<tr>
<th></th>
<th>Sjelden /aldri</th>
<th>1-2 g /uke</th>
<th>3-4 g /uke</th>
<th>5-6 g /uke</th>
<th>Hver dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frokost</td>
<td>[ ]</td>
<td></td>
<td></td>
<td></td>
<td>[ ]</td>
</tr>
<tr>
<td>Formiddagsmat</td>
<td>[ ]</td>
<td>[ ]</td>
<td></td>
<td></td>
<td>[ ]</td>
</tr>
<tr>
<td>Varm middag</td>
<td>[ ]</td>
<td></td>
<td>[ ]</td>
<td></td>
<td>[ ]</td>
</tr>
<tr>
<td>Kveldsmat</td>
<td>[ ]</td>
<td>[ ]</td>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Annet måltid</td>
<td>[ ]</td>
<td></td>
<td>[ ]</td>
<td></td>
<td>[ ]</td>
</tr>
<tr>
<td>Nattmat (kl. 24-06)</td>
<td>[ ]</td>
<td>[ ]</td>
<td></td>
<td></td>
<td>[ ]</td>
</tr>
</tbody>
</table>
46. Hva slags fett bruker du oftest? *(Sett ett kryss pr. linje)*

<table>
<thead>
<tr>
<th></th>
<th>Meierismør</th>
<th>Hard margarin</th>
<th>Myk/lett margarin</th>
<th>Oljer</th>
<th>Bruker ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>På brød</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I matlaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

47. Hvor ofte spiser du vanligvis disse matvarene? *(Sett ett kryss pr linje).*

<table>
<thead>
<tr>
<th></th>
<th>0-3 ganger pr mnd</th>
<th>1-3 ganger pr. uke</th>
<th>4-6 ganger pr. uke</th>
<th>1 gang pr. dag</th>
<th>2 ggr el mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frukt/bær</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grønnsaker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sjokolade/smågodt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kokte poteter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pasta/ris</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pølser/hamburgere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fet fisk</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><em>(f.eks. laks, ørret, sild, makrell som pålegg/middag)</em></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

48. Bruker du følgende kosttilskudd? *(Sett ett kryss for hvert kosttilskudd)*

<table>
<thead>
<tr>
<th></th>
<th>Ja, daglig</th>
<th>Av og til</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tran</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3-kapsler</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin- og/eller mineraltilskudd</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
49. Hvor mange glass drikker du vanligvis av følgende? ½ liter = ca. 3 glass (sett ett kryss pr. linje). Melk i kaffe/te skal og regnes med.

<table>
<thead>
<tr>
<th>Sjelden eller aldri</th>
<th>1-6 glass pr. uke</th>
<th>1 glass pr. dag</th>
<th>2-3 glass pr. dag</th>
<th>4 glass eller mer pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vann, farris o.l.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Helmelk (søt/sur)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Annen melk (søt/sur)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Brus/saft med sukker</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Brus/saft uten sukker</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Juice eller nektar</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

50. Hvor mange kopper kaffe/te drikker du pr. døgn?
(Sett 0 hvis du ikke drikker kaffe/te daglig)

- Filterkaffe, antall kopper
- Kokekaffe/presskanne, antall kopper
- Espresso, cappuccino, caffè latte o.l.
- Svart te, antall kopper
- Grønn te, antall kopper
TOBAKK

51. Røyker du?

- **Nei, jeg har aldri røukt** □
- **Nei, jeg har sluttet å røyke** □
- **Ja, sigaretter daglig** □
- **Ja, sigaretter av og til (fest/ferie, ikke daglig)** □
- **Ja, sigarer/sigarillos/pipe daglig** □
- **Ja, sigarer/sigarillos/pipe av og til** □

Svar på dette hvis du nå røyker daglig eller tidligere har røukt daglig:

- Hvor mange sigaretter røyker eller røykte du vanligvis daglig? __________
- Hvor gammel var du da du begynte å røyke daglig? __________
- Hvis du tidligere har røukt daglig, hvor gammel var du da sluttet? __________

Svar på dette hvis du røyker av og til, eller tidligere har røykt av og til, men ikke daglig:

- Hvor mange sigaretter røyker eller røykte du vanligvis i måneden? __________
- Hvor gammel var du da du begynte å røyke av og til? __________
- Hvis du tidligere har røukt av og til, hvor gammel var du da du sluttet? __________

52. Bruker du, eller har du brukt, snus?

- **Nei, aldri** □
- **Ja, av og til** □
- **Ja, daglig** □

**Hvis ja**, hvor gammel var du da du begynte med snus? __________

**Hvis ja**, hvor mange esker snus bruker/brukte du pr. måned? __________
ALKOHOL

56. Omtrent hvor ofte har du i løpet av de siste 12 måneder drukket alkohol? *Sett ett kryss.* (Regn ikke med lettøl)

- 4-7 ganger pr. uke
- 2-3 ganger pr. uke
- Ca. 1 gang pr. måned
- Noen få ganger pr. år
- Ingen ganger siste år
- Aldri drukket alkohol

57. Har du drukket alkohol i løpet av de siste 4 uker?

- Ja
- Nei

Hvis ja, har du drukket så mye at du har kjent deg sterkt beruset (full)?

- Nei
- Ja, 1-2 ganger
- Ja, 3 ganger eller mer

58. Hvor mange glass (enheter) øl, vin eller brennevin drikker du vanligvis i løpet av 2 uker? (Regn ikke med lettøl) (Sett 0 hvis du ikke drikker alkohol)

Antall glass: Øl: _______ Vin: _______ Brennevin: _______

59. Hvor ofte drikker du 5 glass eller mer øl, vin eller brennevin ved samme anledning?

- Aldri
- Sjeldnere enn månedlig
- Månedlig
- Ukentlig
- Daglig

*Takk for at du tok deg tid til å fylle ut skjemaet!*
Appendix II
ACE 1950 - Akershus hjerteundersøkelse
Spørreskjema om forstyrrelser i hjerterytmen

Dette skjemaet besvares av deltakere som har svart positivt på spørsmål om atrieflimmer eller andre rytmeforstyrrelser i ACE 1950 hovedskjema (spørsmål 18-19).

1. Hvor gammel var du da første gang vite at du hadde atrieflimmer ("hjerteflimmer") eller annen hjerterytmeforstyrrelse?

___________________________ (angi ca. alder)

2. Hvilken kategori passer best for å beskrive atrieflimmer eller annen hjerterytmeforstyrrelse hos deg, slik du har opplevd dette det siste året? (sett kun ett kryss)

☐ Ingen symptomer
☐ Milde symptomer – normal daglig aktivitet ikke påvirket
☐ Uttalte symptomer – normal daglig aktivitet påvirket
☐ Invalidiserende symptomer – normal daglig aktivitet ikke mulig

3. Hvilket alternativ beskriver best hvordan du opplever atrieflimmer (eller en annen hjerterytmeforstyrrelse) hos deg?

☐ Har kun hatt ett anfall siste året eller gjennom hele livet
☐ Anfallsvis atrieflimmer (eller annen hjerterytmeforstyrrelse)
☐ Permanent/kontinuerlig atrieflimmer (eller annen hjerterytmeforstyrrelse)
☐ Vet ikke

4. Hvis du har anfallsvis atrieflimmer eller annen hjerterytmeforstyrrelse, hvor ofte har du anfall?

______________________________

______________________________

______________________________

ACE 1950 – Q-AF - spørreskjema om forstyrrelser i hjerterytmen – versjon 1.3 – 20.08.2013
5. Hvis du har anfallvis atrieflimmer eller annen hjerterytmeforstyrrelse, hvordan går anfallene over?

- De går over av seg selv
- De går over etter at jeg har tatt medisiner (angi type medisin i kommentarfelt)
- De går over kun hvis jeg blir elektrokonvertert (elektrisk støt mot brystveggen)
- Annet

Kommentarer: ____________________________
________________________________________
________________________________________


________________________________________
________________________________________

7. Har du fått behandling med elektrokonvertering (elektrisk støt mot brystveggen)?

- Ja
- Nei

8. Hvis ja, hvor mange ganger har du blitt elektrokonvertert?

________________________________________

9. Hvis ja, når ble du elektrokonvertert første gang (angi ca. alder)?

________________________________________

10. Har du fått ablasjonsbehandling på grunn av din atrieflimmer (eller på grunn av annen hjerterytmeforstyrrelse)?

- Ja
- Nei

11. Hvis ja, hvor mange ganger?

________________________________________

12. Hvis ja, når ble det gjort ablasjon første gang (angi ca. alder)?

________________________________________

13. Hvis ja, hvor ble ablasjon utført?

________________________________________
________________________________________

14. Hvis ja, hvilket utsagn passer best for deg nå?

- Jeg er helt kvitt mine plager med atrieflimmer (eller annen hjerterytmeforstyrrelse)
- Jeg har sjeldne anfall som begrenser meg lite/ingenting i min daglige aktivitet
- Jeg har svært ofte anfall, og disse begrenser min daglige aktivitet.
- Annet:

________________________________________
Prevalence of atrial fibrillation and cardiovascular risk factors in a 63–65 years old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study

Trygve Berge,1,2 Magnus Nakrem Lyngbakken,2,3 Håkon Ihle-Hansen,1,2 Jon Brynildsen,2,3 Mohammad Osman Pervez,2,3 Erika Nerdrum Aagaard,2,3 Thea Vigen,2,3 Brede Kvivik,2,3 Ingrid Elisabeth Christophersen,1 Kjetil Steine,2,3 Torbjørn Omland,2,3 Pål Smith,2,3 Helge Rosjo,2,3 Arnbjot Tveit1,2

ABSTRACT

Objectives To investigate the sex-specific prevalence of atrial fibrillation (AF), including subclinical AF found by screening in a general population aged 63–65 years. The prevalence of cardiovascular risk factors and their association with AF will also be investigated.

Design Cross-sectional analysis of an observational, prospective, longitudinal, population-based cohort study.

Setting General population in Akershus county, Norway.

Participants Women and men born in 1950. We included 3706 of 5827 eligible individuals (63.6%); 48.8% were women.

Methods All participants underwent extensive cardiovascular examinations, including 12-lead ECG.

History of AF and other cardiovascular diseases were self-reported. Subsequent validation of all reported or detected AF diagnoses was performed.

Results Mean age was 63.9±0.7 years. Prevalence of ECG-verified AF was 4.5% (women 2.4%, men 6.4%; p<0.001), including screen-detected AF in 0.3% (women 0.1%, men 0.6%; p<0.01). Hypertension was found in 62.0% (women 57.8%, men 66.0%; p<0.001). Overweight or obesity was found in 67.6% (women 59.8%, men 74.9%; p<0.001). By multivariate logistic regression, risk factors associated with AF were height (OR 1.67 per 10 cm; 95% CI 1.26 to 2.22; p<0.001), weight (OR 1.15 per 10 kg; 95% CI 1.01 to 1.30; p=0.03), hypertension (OR 2.49; 95% CI 1.61 to 3.86; p<0.001), heart failure (OR 3.51; 95% CI 1.71 to 7.24; p=0.001), reduced estimated glomerular filtration rate (OR 2.56; 95% CI 1.42 to 4.60; p<0.01) and at least one first-degree relative with AF (OR 2.32; 95% CI 1.63 to 3.31; p<0.001), whereas male sex was not significantly associated (OR 1.00; 95% CI 0.59 to 1.68; p=0.99).

Conclusion In this cohort from the general population aged 63–65 years, we found a higher prevalence of known AF than previously reported below the age of 65 years. The additional yield of single time point screening for AF was low. Body size and comorbidity may explain most of the sex difference in AF prevalence at this age.

Trial registration number NCT01555411; Results.

INTRODUCTION

The prevalence of atrial fibrillation (AF) is on the rise and this arrhythmia is emerging as a major public health problem due to the associated stroke risk and related costs.1 2 The prevalence in the adult population has been estimated to be 1%–2%, but is probably as high as 2%–3%, based on recent data.3 Previous studies in specific age groups have reported a prevalence of AF of 4.2% among subjects 60–69 years of age.4 The increase in prevalence is most likely due to both ageing of the population and improved survival from other types of cardiovascular disease (CVD). Increased awareness and improved detection of subclinical AF may also be contributing factors.

Screening for AF has received increased attention lately. European guidelines recommend opportunistic screening by pulse palpation or ECG in all patients >65 years of age.4 Despite the emergence of technology for
ambulant ECG monitoring, current recommendations are still based on single time point screening by standard ECG, enabling undetected AF to be diagnosed in 1.4% of the population ≥65 years. At this age and above, one or more additional risk factors for stroke, according to the CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65-74, and Sex (female)) score, provide a strong indication for anticoagulation. Hence, subjects with hypertension, diabetes or other risk factors for stroke represent a potential target group for screening for AF. Studies have shown that about 50% of incident AF could be attributed to elevated levels of risk factors for AF, of which elevated blood pressure and overweight were the most important contributors. This raises the issue of early detection and subsequent ‘upstream’ treatment of these conditions.

The primary objective of this study was to investigate the sex-specific prevalence of self-reported and ECG-validated AF, including subclinical AF found by screening, in a contemporary population-based cohort aged 63–65 years. Secondary objectives were to investigate the prevalence of cardiovascular risk factors and their association with AF.

### METHODS

#### Study population

The Akershus Cardiac Examination (ACE) 1950 Study is an observational, longitudinal, population-based cohort study of individuals born in 1950. The identity of all permanent residents of Akershus county born in 1950 were retrieved from the Norwegian Population Registry at the start of the study (n=5827). These were invited by letter and subsequent phone calls. Design and general methodology have been reported previously. In this article, we present data from a cross-sectional analysis of the baseline examination, performed in the period September 2012–May 2015.

#### Study variables

Clinical data included measurements of height, weight, seated blood pressure and 12-lead ECG. Body mass index (BMI) was calculated according to the standard formula (kg/m²), and categorised into overweight (BMI 25.0–29.9 kg/m²) and obesity (BMI ≥30.0 kg/m²). Body surface area (BSA; m²) was calculated by the Mosteller formula. A web-based questionnaire for registration of medical history and lifestyle was used. The questionnaire was formulated in the same manner as in previous large Norwegian population studies, and participants were urged to ask study personnel at the baseline visit if they were not able to respond adequately to all questions, to ensure high-quality data collection. Daily use of all types of medication was registered according to the Anatomical Therapeutic Chemical Classification System.

Concerning AF, the participants were asked: ‘Have you ever been diagnosed with atrial fibrillation or atrial flutter?’ All self-reported AF were validated according to the following: (1) ECG documentation of AF or atrial flutter according to standard definitions, and if such was not available, (2) a solid description of AF or atrial flutter in the medical record (ie, direct current cardioversion or AF ablation procedure). All ECGs and medical records were evaluated by two physicians, of whom one was a cardiologist. Available information in the medical records including ECGs, as well as the study ECG, was used to classify AF as paroxysmal versus persistent/permanent. Participants without history of AF, but in whom AF was detected in the study ECG, were classified as previously undiagnosed AF. Participants also reported any familial AF history among first-degree relatives. For individuals with AF, we calculated the CHA2DS2-VASc stroke risk score. This was based on the presence or history of heart failure, hypertension, diabetes, stroke/transient ischaemic attack (TIA), myocardial infarction, age ≥65 years and female sex.

Hypertension was defined as the mean (from the second and third of three readings) systolic blood pressure ≥140 mm Hg or mean diastolic blood pressure ≥90 mm Hg, or current use of any antihypertensive medication. The diagnoses of heart failure, myocardial infarction and stroke or TIA were self-reported. Coronary artery disease was defined as self-reported myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting surgery.

Fasting blood samples were analysed on site and included lipids, blood glucose, haemoglobin A1c (HbA1c) and serum creatinine. The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate estimated glomerular filtration rate (eGFR). Reduced eGFR (eGFR <60 mL/min/1.73 m²), indicative of chronic kidney disease, was reported and used for the analyses. Hypercholesterolaemia was defined as total cholesterol ≥2.6 mmol/L and/or low-density lipoprotein (LDL) ≥4.1 mmol/L and/or use of lipid-lowering medication. Diabetes was defined as a self-reported diagnosis or use of hypoglycaemic medication or elevated glucose tests (both HbA1c ≥6.5% and fasting blood glucose ≥7.0 mmol/L).

Higher education was defined as >12 years of formal education, that is, college/university education at any level. Alcohol consumption, smoking and physical activity were self-reported. Physical activity was classified according to a previously validated model (details provided in online supplementary table 1).

The data are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The study complies with the Declaration of Helsinki, and written informed consent was obtained from all participants.

### Statistical analysis

Continuous variables are reported as mean and SD, and Student’s t-test was used for between-group analysis. Continuous variables not normally distributed are reported as median with IQR and analysed with the...
Mann-Whitney U test. Categorical variables are presented as counts and/or proportions (%) and compared by the χ² test or Fisher’s exact test as appropriate. Logistic regression analysis was used to assess associations between risk factors and AF. All available known risk factors for AF were selected from univariate analyses based on clinical and statistical significance (p value <0.20). Pearson correlation, as well as multicollinearity statistics, was run between each of the independent variables before inclusion in a multivariate logistic regression model. To assess the robustness of the model, we performed a sensitivity analysis in which all candidate variables were put into the same model. Secondary analyses replacing height and weight with the more commonly used BMI, as well as BSA, were also performed. P values are two-sided and considered significant when <0.05. Cases with missing data were omitted from descriptive statistics of that particular variable. Hence, the reported proportions represent the valid proportions. As for the regression analysis, a complete case analysis was performed. Statistics were performed using IBM SPSS Statistics for Windows, V.24.0 (IBM Corp., Armonk, New York, USA).

Patient and public involvement
The participants of this study represent a large age cohort from the general population. Although there was no public or participants’ involvement in the planning and design of the study, random samples of participants were, during the conduct of the baseline examinations, invited to respond to a questionnaire focusing on how they perceived their participation in the study, and if they had any suggestions to improve the study conduct. Individual study results (blood pressure, cholesterol levels, etc.) were sent to all study participants shortly after their study visit, accompanied by individual advice in case any further follow-up was recommended. All scientific study results are continuously communicated to the participants as well as the general population through local media and our own website www.ace1950.no. Newsletters with updated study information have also been sent to all study participants by mail. A ‘participant advisory board’ is now currently being formalised, and will be involved in the planning of further follow-up studies of this cohort.

RESULTS

General cohort profile
A total of 3706 participants (from 5827 eligible residents; 63.6% participation rate) were enrolled and examined in the ACE 1950 Study. Women and men were evenly represented, with 1807 (48.8%) women and 1899 (51.2%) men (participation rate 63.7% among women, 63.5% among men; p=0.86). Akershus University Hospital enrolled 2473 participants, and Bærum Hospital (Vestre Viken Hospital Trust) 1235 participants, within their respective catchment areas. The majority were of Caucasian ethnicity (3624; 97.8%). All participants were born in 1950, and the mean age at inclusion was 63.9±0.7 years.

Baseline characteristics are presented in table 1. The prevalence of CVD and cardiovascular risk factors were generally higher in men than in women, with the exception that a higher number of women had hypercholesterolaemia (p<0.01). There were no sex differences in reported daily smoking (15.3% of women vs 13.7% of men; p=0.19). As shown in table 1, the majority of the cohort was overweight or obese. Obesity was found in 22.6% (24.1% of men, 21.1% of women; p=0.03).

Prevalence of known and unknown AF
A flowchart illustrating the validation of AF is shown in figure 1. History of AF was reported by 193 (5.2%) participants. After validation, 153 (4.1%) had a verified AF diagnosis. Hence, the positive predictive value (PPV) of self-reported AF, compared with the direct review of medical records and ECGs, was 79.3%. Previously unknown AF was diagnosed by ECG in 12 (0.3%) participants. The total prevalence of validated AF was 4.5% (n=165; 2.4% among women, 6.4% among men; p<0.001), as shown in figure 1 and table 2. Nine subjects had a history of atrial flutter (or atrial flutter in study ECG), without any previous diagnosis of AF. These were counted as AF. Permanent AF was identified in 48 cases (table 2).

Clinical characteristics of AF
Table 3 shows sex-specific characteristics of individuals with AF compared with the rest of the cohort. Both women and men with AF were significantly taller and heavier than those without AF. Other measures of body size, such as waist and hip circumference, and BSA, were also higher among individuals with AF, regardless of sex. Obesity was found in 41.8% of participants with AF versus 21.7% in unaffected participants (p<0.001). Hypertension, heart failure and reduced eGFR were more prevalent in individuals with AF of both sexes, whereas coronary heart disease was more prevalent only among men with AF. Otherwise, there were only minor sex differences. With regard to level of physical activity, there were no significant differences between the groups.

A higher number of both women and men with AF reported a first-degree relative with known AF, compared with the rest of the cohort (33.9% vs 19.2%; p<0.001; table 3). Familial AF was more prevalent in women with AF than in men with AF (56.8% vs 25.6%; p<0.001).

Risk factors for AF
Risk factors associated with AF, assessed by logistic regression, are reported in table 4. In univariate analysis, male sex was associated with increased likelihood of having AF. However, in multivariate analysis, sex was not associated with AF, when adjusting for height, weight and other risk factors. Height, weight, hypertension, heart failure, reduced eGFR and family history of AF were all significantly associated with AF in multivariate analysis. A sensitivity analysis, in which all independent variables were included, did not change the results (see online...
supplementary table 2). In secondary analyses, height and weight were replaced with BMI or BSA. In these analyses, male sex remained significantly associated with AF, and a strong association to AF was found for both BMI and BSA, while only minor changes were seen for other variables (data not shown).

<table>
<thead>
<tr>
<th></th>
<th>Total n=3706</th>
<th>Men n=1899</th>
<th>Women n=1807</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>63.9±0.7</td>
<td>63.9±0.7</td>
<td>63.9±0.6</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Caucasian ethnicity</strong></td>
<td>97.8</td>
<td>97.4</td>
<td>98.2</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Higher education</strong></td>
<td>46.4</td>
<td>50.2</td>
<td>42.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>27.2±4.4</td>
<td>27.7±4.0</td>
<td>26.6±4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Overweight/obesity (BMI ≥25)</strong></td>
<td>67.6</td>
<td>74.9</td>
<td>59.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td>138±19</td>
<td>139±18</td>
<td>137±20</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
<td>77±10</td>
<td>80±10</td>
<td>74±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>62.0</td>
<td>66.0</td>
<td>57.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>4.3</td>
<td>7.4</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td>7.1</td>
<td>11.5</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>1.6</td>
<td>2.3</td>
<td>0.9</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>4.5</td>
<td>6.4</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stroke/TIA</strong></td>
<td>3.8</td>
<td>5.0</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>8.6</td>
<td>11.6</td>
<td>5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Reduced eGFR</strong></td>
<td>3.9</td>
<td>3.4</td>
<td>4.3</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Hypercholesterolaemia</strong></td>
<td>52.6</td>
<td>50.6</td>
<td>54.7</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>7.2</td>
<td>6.9</td>
<td>7.4</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Obstructive sleep apnoea</strong></td>
<td>6.2</td>
<td>9.0</td>
<td>3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Current daily smoking</strong></td>
<td>14.5</td>
<td>13.7</td>
<td>15.3</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Current or former daily smoking</strong></td>
<td>61.8</td>
<td>62.2</td>
<td>61.5</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Daily moist tobacco (‘snus’)’</strong></td>
<td>2.2</td>
<td>3.8</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;14 standard drinks/week</td>
<td>2.8</td>
<td>4.3</td>
<td>1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>‘Binge drinking’</td>
<td>16.3</td>
<td>25.3</td>
<td>6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Physical activity level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>19.1</td>
<td>22.5</td>
<td>15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>19.7</td>
<td>19.7</td>
<td>19.7</td>
<td>0.98</td>
</tr>
<tr>
<td>Medium</td>
<td>40.3</td>
<td>34.7</td>
<td>46.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>21.0</td>
<td>23.1</td>
<td>18.8</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular medication (ATC C)</td>
<td>46.1</td>
<td>50.0</td>
<td>41.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics (ATC C03)</td>
<td>3.1</td>
<td>2.9</td>
<td>3.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Beta blockers (ATC C07)</td>
<td>13.4</td>
<td>16.7</td>
<td>9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium channel blockers (ATC C08)</td>
<td>8.1</td>
<td>9.7</td>
<td>6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Agents acting on the renin-angiotensin system (ATC C09)</td>
<td>26.9</td>
<td>30.6</td>
<td>23.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-modifying agents (ATC C10)</td>
<td>26.2</td>
<td>29.6</td>
<td>22.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Categorical variables are reported as percentages. Continuous variables are presented as mean±SD. P values indicate difference between sexes. Higher education: ≥12 years of formal education.
‘Binge drinking’ is defined as heavy episodic drinking (at least five standard drinks of alcohol) at least once per month. Details for classification of physical activity level are provided in online supplementary table 1. Medication: self-reported cardiovascular medication according to ATC classification.
ATC, Anatomical Therapeutic Chemical; BMI, body mass index (kg/m²); COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; TIA, transient ischaemic attack.
Stroke risk in AF

The median CHA$_2$DS$_2$-VASc stroke risk score among AF subjects was 1 (IQR 1–2) in men and 2 (IQR 2–2) in women (see online supplementary table 3). In total, 83.6% in the AF group fulfilled our criteria for hypertension. As many as 41.1% of individuals with AF had elevated blood pressure (≥140/≥90 mm Hg) at the ACE 1950 baseline visit, regardless of ongoing treatment. Details of stroke risk and medication in individuals with AF are presented in online supplementary table 3. Furthermore, characteristics of screen-detected AF (n=12) are shown in online supplementary table 4. These individuals were generally low risk; the median CHA$_2$DS$_2$-VASc score was 1 (total range 0–2). However, 75.0% were overweight and 66.7% had hypertension.

Missing data

Basic clinical variables, including height, weight and ECG were available from all 3706 participants, whereas blood pressure was missing in only two participants. Data was missing for <1% of the participants for all reported variables, including all self-reported CVD, except for physical activity in which 2.3% (n=84) had missing data on at least one of three physical activity questions.

DISCUSSION

Principal findings

The key results of this study were that we identified a high prevalence of verified AF, whereas single time point screening by 12-lead ECG identified only 0.3% new cases in an unselected contemporary population aged 63–65 years. Body size and cardiovascular comorbidity, but not sex, were independently associated with prevalent AF at this age.

Strengths and limitations

Strengths of this study include the unselected population-based design and complete, or nearly complete, data...
Limitations include uncertainty about the accuracy of self-reported CVD. In particular, we believe heart failure and history of stroke have a high degree of uncertainty, whereas diseases such as diabetes and myocardial infarction may be more easily defined and recognised in the population. The diagnosis of hypertension should, ideally, be based on serial or ambulant blood pressure measurements. Hence, the prevalence may be overestimated.

Negative responses to self-reported AF were not validated. However, this may only have led to an underestimation of the prevalence, due to the unknown number of false negative responses. A validation of self-reported AF in the Nord-Trøndelag Health Study (HUNT) questioned the use of self-reported AF, as sensitivity was low and many AF cases were missed.

Our study was not designed as a

<table>
<thead>
<tr>
<th>Table 3: Clinical characteristics of study population by AF prevalence and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
</tr>
<tr>
<td>Body surface area, m²</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Stroke/TIA</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Reduced eGFR</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>No comorbidity*</td>
</tr>
<tr>
<td>Hospitalisation last 12 months</td>
</tr>
<tr>
<td>Current daily smoking</td>
</tr>
<tr>
<td>Familial AF†</td>
</tr>
<tr>
<td>Higher education‡</td>
</tr>
<tr>
<td>Physical activity level</td>
</tr>
<tr>
<td>Inactive</td>
</tr>
<tr>
<td>Low/medium</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Heart rate§</td>
</tr>
<tr>
<td>PQ interval¶</td>
</tr>
<tr>
<td>QRS duration¶</td>
</tr>
</tbody>
</table>

Categorical variables are reported as counts with percentages in parentheses. Continuous variables are reported as mean±SD. P values indicate difference between AF and non-AF (within each sex).

*No comorbidity: neither hypertension, coronary heart disease, heart failure, stroke, diabetes, reduced eGFR, obstructive sleep apnoea nor obesity.

†Familial AF: self-report of at least one first-degree relative with known AF.

‡Higher education: ≥12 years of formal education.

§Heart rate: beats per minute in 12-lead ECG.

¶PQ interval and QRS duration are reported in ms. For heart rate, PQ interval and QRS duration, all subjects with AF in study ECG were excluded (n=60).

AF, atrial fibrillation; BMI, body mass index, kg/m²; eGFR, estimated glomerular filtration rate; TIA, transient ischaemic attack.
validation study and therefore sensitivity and specificity of self-reported AF could not be estimated. Still, the PPV of self-reported AF in our study, 79.3%, was much higher than found in the HUNT study (PPV 56%).

Furthermore, classification of AF as paroxysmal or persistent/permanent was made based on available ECGs and medical records, and we cannot rule out that some individuals may have been misclassified.

By its design, our study depicts a limited age group, making comparison to other studies difficult. Finally, the study was designed as a cardiovascular cohort study with a special focus on AF. Hence, individuals with known AF may have been more motivated to participate than unaffected individuals, which may represent a selection bias.

### Prevalence of AF

To the best of our knowledge, no other study based on unselected population data has reported a prevalence of AF as high as 4.5% below the age of 65 years. Most comparable studies have reported a prevalence of 3.7%–4.2% in the age group 60–69 years. A Swedish study found 2.9% in the more comparable age group 60–64 years, while the Rotterdam study reported <2% in this age group. AF prevalence in our study is particularly high for men (6.4%), while a few studies have reported a prevalence >2.4% among women at this age.

### Single time point screening for AF

The true prevalence of AF cannot be found by single time point ECGs, as some cases will be missed due to the paroxysmal nature of the arrhythmia. Still, opportunistic single time point screening is recommended in current guidelines. However, this is based on studies in which single time point screening typically identified 1.0%–1.6% unknown AF by methods comparable to our study.

The lower yield of screening in our study may partly be explained by the high prevalence of known AF, and the fact that the population under study has a high level of education and lives in a setting with good access to healthcare and primary care in particular. The population examined was just below 65 years. Hence, our findings confirm that yield of screening in this age group is low. While some studies with similar population-based design have found comparable low rates of new AF, others have shown a much higher yield by more extensive methods such as intermittent or continuous ECG registrations. The large discrepancies between studies supports the recommendation that future AF screening should be country specific and health system specific.

A recent white paper on AF screening concluded that screen-detected AF found on single time point screening

### Table 4 Risk factors associated with atrial fibrillation (AF)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate OR (95% CI)</th>
<th>P value</th>
<th>Multivariate OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2.73 (1.92 to 3.87)</td>
<td>&lt;0.001</td>
<td>1.00 (0.59 to 1.68)</td>
<td>0.99</td>
</tr>
<tr>
<td>Height per 10 cm</td>
<td>1.90 (1.59 to 2.28)</td>
<td>&lt;0.001</td>
<td>1.67 (1.26 to 2.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight per 10 kg</td>
<td>1.42 (1.29 to 1.55)</td>
<td>&lt;0.001</td>
<td>1.15 (1.01 to 1.30)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>3.27 (2.15 to 4.97)</td>
<td>&lt;0.001</td>
<td>2.49 (1.61 to 3.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8.53 (4.71 to 15.48)</td>
<td>&lt;0.001</td>
<td>3.51 (1.71 to 7.24)</td>
<td>0.001</td>
</tr>
<tr>
<td>Familial AF†</td>
<td>2.16 (1.55 to 3.02)</td>
<td>&lt;0.001</td>
<td>2.32 (1.63 to 3.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced eGFR</td>
<td>2.87 (1.66 to 4.95)</td>
<td>&lt;0.001</td>
<td>2.56 (1.42 to 4.60)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2.88 (1.88 to 4.41)</td>
<td>&lt;0.001</td>
<td>1.56 (0.95 to 2.57)</td>
<td>0.08</td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td>2.09 (1.13 to 3.86)</td>
<td>0.02</td>
<td>1.43 (0.74 to 2.78)</td>
<td>0.29</td>
</tr>
<tr>
<td>OSA</td>
<td>1.94 (1.17 to 3.23)</td>
<td>0.01</td>
<td>1.11 (0.63 to 1.97)</td>
<td>0.71</td>
</tr>
<tr>
<td>Physical activity (low/normal as ref.‡)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>1.61 (1.10 to 2.37)</td>
<td>0.02</td>
<td>1.38 (0.92 to 2.07)</td>
<td>0.12</td>
</tr>
<tr>
<td>High level</td>
<td>1.30 (0.88 to 1.94)</td>
<td>0.19</td>
<td>1.20 (0.80 to 1.81)</td>
<td>0.38</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.24 (0.74 to 2.08)</td>
<td>0.41</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>0.72 (0.44 to 1.19)</td>
<td>0.20</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>High alcohol consumption§</td>
<td>0.81 (0.45 to 2.78)</td>
<td>0.81</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Variables with p<0.20 in univariate logistic regression analysis are included in the multivariate analysis (a complete analysis of all candidate variables are included in online supplementary table 2).

Bold font indicates a significant association in multivariate analysis.

*Hypertension: mean systolic blood pressure ≥140 mm Hg, or mean diastolic blood pressure ≥90 mm Hg, or current use of any antihypertensive medication.

†Familial AF: self-report of at least one first-degree relative with known AF.

‡Physical activity (PA) level: Inactive and high level of PA compared with low/medium PA (combined to one group) as the reference group.

§High alcohol consumption: >14 standard drinks/week (both sexes).

eGFR, estimated glomerular filtration rate; OSA, obstructive sleep apnoea; TIA, transient ischaemic attack.

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should be considered for stroke prevention in the same manner as clinical AF. More extensive screening methods should be considered in selected groups, particularly in those >65 years and with additional risk factors. Although alternative methods such as dedicated blood pressure devices have shown promising results as a primary step in screening, ECG confirmation is still mandated for the diagnosis of AF.

Risk factors for AF
Apart from age, hypertension has been accepted as the most important risk factor for AF for decades, largely due to its high occurrence in the general population. More recent data have shown, however, that the risk in both sexes may be higher from obesity. Similar trends have been found in the Framingham Heart Study, in which diabetes and increased BMI have been identified as emerging risk factors.

Height has been demonstrated to be a risk factor for AF and other CVD, independent from weight. It has also been shown that use of BMI as a measure of body size leads to loss of predictive information, compared with weight and height separately. Most studies, including ours, have found that age-adjusted prevalence of AF is higher in men than in women. Still, male sex was, in our study, not associated with AF after assessing the impact of height, weight and other risk factors. This may indicate that differences in the distribution of AF risk factors, including body height and weight, may account for most, if not all, of the higher prevalence of AF in men at this age. This is consistent with findings from three large cohorts resulting in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AF risk score for AF prediction, in which height and weight, but not sex, were found to predict AF.

In our study, we found that most AF subjects were defined as hypertensive, nearly half were obese, and only 13% had no known comorbidity. The rising prevalence of obesity during the last decades may have contributed to an increasing AF prevalence. Our findings support this theory; however, we cannot draw any conclusions based on our limited data.

The heritability of AF is well established. For many individuals with AF, the arrhythmia is probably a multifactorial and polygenic phenomenon, and a number of genetic variants associated with increased risk have been identified. Some studies have also shown a strong association between self-reported familial AF and AF occurrence, independent of other risk factors, including genetic variants. In line with these studies, we found that AF occurred twice as often in subjects who had at least one first-degree relative with AF, at any age, compared with those without familial AF.

Stroke risk in AF
Stroke prevention is of utmost importance in AF, and guideline adherence improves outcomes. In this cohort, stroke risk in the AF group was low (see online supplementary table 3). Use of anticoagulation was reported only in 47% of individuals with AF. However, many turned 65 years shortly after inclusion and their indication for anticoagulation would then have been strengthened. Within the small group of individuals with screen-detected AF, the stroke risk was even lower.

Clinical implications
Increased awareness with regard to detection and treatment of AF is desirable, particularly because of the increased stroke risk. However, it is still unknown whether screening or more active case finding for AF will be effective in reducing stroke rates. Current guidelines advise health personnel to carry out simple measures such as pulse palpation and 12–lead ECG more frequently at the age of 65 years and above, or even in younger age groups if risk factors for stroke are present. New and portable single-lead ECG devices may make these recommendations easier to implement, as single time point or even repeated measurements can be performed more easily. However, it is still unknown in which groups of the population screening may be justified. The low yield of single time point screening in our study supports the opinion that screening below the age of 65 years may only be recommended in selected high-risk groups.

The high prevalence of obesity and untreated hypertension found in this cohort is alarming. These conditions can potentially be prevented in primary care and by public health measures. Prevention of AF by early detection and treatment of these conditions may be as important as early detection of AF itself. Nearly half of AF individuals in this study were found with elevated blood pressure, regardless of treatment, underlining a potential also for improved treatment within this group.

CONCLUSION
The prevalence of known AF was higher than previously reported below the age of 65 years, and higher in men than in women. Single time point screening for AF revealed a low number of previously unknown AF. Height, weight and comorbidity, but not sex, were independently associated with AF at this age.
work) received honoraria or research support from Abbott, AstraZeneca, Bayer, Novartis, Roche, Singulex and Thermo Fisher. HR has (outside this work) received honoraria or research support from Novartis, CardiNor AS and SpinChip Diagnostics. TO and HR are partners in a patent filed by the University of Oslo regarding the use of secretoneurin as a biomarker in patients with cardiovascular disease and patients with critical illness.

Patient consent Obtained.

Ethics approval Regional Ethics Committee, South-East Norway (ref. 2011/1475).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data set used in this study is not publicly available, as the Data Protection Authority approval and patient consent do not allow for such publication. However, the study group welcomes initiatives for cooperation, and data access may be granted upon application. More information on: www.ace1950.no.

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REFERENCES

### Supplementary Table 1: Questions used for self-reporting of physical activity and calculation of PAI (Physical Activity Index)

<table>
<thead>
<tr>
<th>Physical activity&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td>How frequently do you exercise? Give an average (by exercise we mean, for example, going for walks, skiing, swimming or training/sport).</td>
</tr>
<tr>
<td>- Never [0]</td>
</tr>
<tr>
<td>- Less than once a week [0]</td>
</tr>
<tr>
<td>- Once a week [1]</td>
</tr>
<tr>
<td>- 2-3 times per week [2.5]</td>
</tr>
<tr>
<td>- Almost every day [5]</td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
</tr>
<tr>
<td>If you do such exercise as frequently as once or more times a week: How hard do you push yourself? (Give an average)</td>
</tr>
<tr>
<td>- I take it easy without breaking into a sweat or losing my breath [1]</td>
</tr>
<tr>
<td>- I push myself so hard that I lose my breath and break into a sweat [2]</td>
</tr>
<tr>
<td>- I push myself to near-exhaustion [3]</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
</tr>
<tr>
<td>How long does each session last? (Give an average)</td>
</tr>
<tr>
<td>- Less than 15 minutes [0.1]</td>
</tr>
<tr>
<td>- 16-30 minutes [0.38]</td>
</tr>
<tr>
<td>- 30 minutes to 1 hour [0.75]</td>
</tr>
<tr>
<td>- More than 1 hour [1]</td>
</tr>
</tbody>
</table>

The response to each question (numbers in clams) was multiplied to calculate a Physical Activity Index (PAI), and this index was used for categorization into four groups:
- Inactive [0]
- Low PA [0.05-1.50]
- Medium PA [1.51-3.75]
- High PA [3.76-15.00]

<sup>1</sup> This 3-item self-reported assessment of physical activity and consequent 4-level Physical Activity Index has been validated in the Norwegian HUNT study (*Nord-Trøndelag health study*), and shown moderate but significant correlation to both measured VO<sub>2max</sub> and to the *International Physical Activity Questionnaire*.

**Reference:**

### Supplementary Table 2: Additional sensitivity analysis for risk factors associated with atrial fibrillation

‘Original model’ as depicted in Table 4 of the manuscript. The ‘complete model’ is an additional analysis including all candidate variables in the same model.

<table>
<thead>
<tr>
<th></th>
<th>Univariate OR (95% CI)</th>
<th>p</th>
<th>Multivariate OR (95% CI) ‘Original model’</th>
<th>p</th>
<th>Multivariate OR (95% CI) ‘Complete model’</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2.73 (1.92 – 3.87)</td>
<td>&lt;0.001</td>
<td>1.00 (0.59 – 1.68)</td>
<td>0.99</td>
<td>1.03 (0.61 – 1.74)</td>
<td>0.92</td>
</tr>
<tr>
<td>Height per 10 cm</td>
<td>1.90 (1.59 – 2.28)</td>
<td>&lt;0.001</td>
<td>1.67 (1.26 – 2.22)</td>
<td>&lt;0.001</td>
<td>1.62 (1.21 – 2.16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight per 10 kg</td>
<td>1.42 (1.29 – 1.55)</td>
<td>&lt;0.001</td>
<td>1.15 (1.01 – 1.30)</td>
<td>0.03</td>
<td>1.16 (1.02 – 1.32)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.27 (2.15 – 4.97)</td>
<td>&lt;0.001</td>
<td>2.49 (1.61 – 3.86)</td>
<td>&lt;0.001</td>
<td>2.47 (1.59 – 3.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8.53 (4.71 – 15.48)</td>
<td>&lt;0.001</td>
<td>3.51 (1.71 – 7.24)</td>
<td>0.001</td>
<td>3.37 (1.61 – 7.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Familial AF</td>
<td>2.16 (1.55 – 3.02)</td>
<td>&lt;0.001</td>
<td>2.32 (1.63 – 3.31)</td>
<td>&lt;0.001</td>
<td>2.35 (1.64 – 3.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced eGFR</td>
<td>2.87 (1.66 – 4.95)</td>
<td>&lt;0.001</td>
<td>2.56 (1.42 – 4.60)</td>
<td>&lt;0.01</td>
<td>2.43 (1.33 – 4.43)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2.88 (1.88 – 4.41)</td>
<td>&lt;0.001</td>
<td>1.56 (0.95 – 2.57)</td>
<td>0.08</td>
<td>1.60 (0.96 – 2.66)</td>
<td>0.07</td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td>2.09 (1.13 – 3.86)</td>
<td>0.02</td>
<td>1.43 (0.74 – 2.78)</td>
<td>0.29</td>
<td>1.49 (0.77 – 2.90)</td>
<td>0.24</td>
</tr>
<tr>
<td>OSA</td>
<td>1.94 (1.17 – 3.23)</td>
<td>0.01</td>
<td>1.11 (0.63 – 1.97)</td>
<td>0.71</td>
<td>1.07 (0.60 – 1.92)</td>
<td>0.82</td>
</tr>
<tr>
<td>Physical activity (low/normal as ref.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>1.61 (1.10 – 2.37)</td>
<td>0.02</td>
<td>1.38 (0.92 – 2.07)</td>
<td>0.12</td>
<td>1.39 (0.92 – 2.11)</td>
<td>0.12</td>
</tr>
<tr>
<td>High level</td>
<td>1.30 (0.88 – 1.94)</td>
<td>0.19</td>
<td>1.20 (0.80 – 1.81)</td>
<td>0.38</td>
<td>1.20 (0.79 – 1.81)</td>
<td>0.39</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.24 (0.74 – 2.08)</td>
<td>0.41</td>
<td>-</td>
<td>-</td>
<td>0.68 (0.39 – 1.20)</td>
<td>0.19</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>0.72 (0.44 – 1.19)</td>
<td>0.20</td>
<td>-</td>
<td>-</td>
<td>0.94 (0.55 – 1.59)</td>
<td>0.81</td>
</tr>
<tr>
<td>High alcohol consumption</td>
<td>0.81 (0.45 – 2.78)</td>
<td>0.81</td>
<td>-</td>
<td>-</td>
<td>0.87 (0.34 – 2.24)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Variables with p<0.20 in univariate logistic regression analysis were included in the original multivariate analysis (‘original model’). Bold font indicates a significant association in multivariate analysis. Hypertension: Mean systolic blood pressure ≥140 mmHg, or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. TIA: Transient ischemic attack. Familial AF: Self-report of at least one 1<sup>st</sup> degree relative with known AF. OSA: Obstructive sleep apnoea. Physical activity (PA) level: Inactive and high level of PA compared to low/medium PA (combined to one group) as the reference group. High alcohol consumption: >14 standard drinks/week (both sexes).
Supplementary Table 3: Stroke risk and use of medication in individuals with atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Total AF (n=165)</th>
<th>Men with AF (n=121)</th>
<th>Women with AF (n=44)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA₂DS₂-VASc score, mean ±SD</td>
<td>1.7 ±1.1</td>
<td>1.4 ±1.0</td>
<td>2.2 ±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score, median [IQR; total range]</td>
<td>2 [1-2; 0-6]</td>
<td>1 [1-2; 0-5]</td>
<td>2 [2-2; 1-6]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc ≥2 (men) or ≥3 (women) (%)</td>
<td>52 (31.5)</td>
<td>45 (37.2)</td>
<td>7 (15.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Elevated blood pressure, (%)</td>
<td>67 (41.1)</td>
<td>46 (38.7)</td>
<td>21 (47.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Anticoagulation, (%)</td>
<td>77 (46.7)</td>
<td>56 (46.3)</td>
<td>21 (47.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Platelet inhibitors, (%)</td>
<td>46 (27.9)</td>
<td>38 (31.4)</td>
<td>8 (18.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Beta-blockers, (%)</td>
<td>97 (58.8)</td>
<td>69 (57.0)</td>
<td>28 (63.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Calcium antagonists, (%)</td>
<td>25 (15.2)</td>
<td>20 (16.5)</td>
<td>5 (11.4)</td>
<td>0.41</td>
</tr>
<tr>
<td>Antiarrhythmic drugs, (%)</td>
<td>28 (17.0)</td>
<td>22 (18.2)</td>
<td>6 (13.6)</td>
<td>0.49</td>
</tr>
<tr>
<td>Class Ic, (%)</td>
<td>19 (11.5)</td>
<td>14 (11.6)</td>
<td>5 (11.4)</td>
<td>0.97</td>
</tr>
<tr>
<td>Class III, (%)</td>
<td>9 (5.5)</td>
<td>8 (6.6)</td>
<td>1 (2.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Digoxin, (%)</td>
<td>4 (2.4%)</td>
<td>3 (2.5)</td>
<td>1 (2.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>ACE inhibitors or ATII antagonists, (%)</td>
<td>63 (38.2)</td>
<td>51 (42.1)</td>
<td>12 (27.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Statins, (%)</td>
<td>63 (38.2)</td>
<td>51 (42.1)</td>
<td>12 (27.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Thyroid hormone therapy, (%)</td>
<td>7 (4.2)</td>
<td>1 (0.8)</td>
<td>6 (13.6)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Categorical variables are reported as counts with percentages in parentheses. Continuous variables are reported as mean ±SD. P-values indicate difference between sexes. CHA₂DS₂-VASc score reported both as mean ±SD and median, including range. IQR: Inter-quartile range. Elevated blood pressure: ≥140 mmHg (systolic) or ≥90 mmHg diastolic regardless of treatment. ACE: Angiotensin converting enzyme. ATII: Angiotensin type 2.
## Supplementary Table 4: Stroke risk and comorbidity in screen-detected AF

<table>
<thead>
<tr>
<th></th>
<th>New AF at screening (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, (%)</td>
<td>11 (91.7)</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score, mean ±SD</td>
<td>1.1 ±0.8</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score, median [total range]</td>
<td>1 [0-2]</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc 0, (%)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc 1, (%)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc 2, (%)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Overweight, (%)</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>Hypertension, (%)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Elevated blood pressure, (%)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Heart failure, (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diabetes, (%)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>History of stroke, (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myocardial infarction, (%)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Reduced eGFR, (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea, (%)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Daily smoking, (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Categorical variables are reported as counts with percentages in parentheses. CHA₂DS₂-VASc score is reported both as mean ±SD and median. Hypertension: Mean systolic blood pressure ≥140 mmHg, or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. Elevated blood pressure: ≥140 mmHg (systolic) or ≥90 mmHg diastolic regardless of treatment. TIA: Transient ischemic attack.